



Original Article

The clinical features of cataplexy: A questionnaire study in narcolepsy patients with and without hypocretin-1 deficiency

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ABSTRACT

Background: Narcolepsy is often not recognized or accurately diagnosed. This may be due to the fact that cataplexy, a core symptom which is virtually 100% specific, can—in practice—only be diagnosed based on the patient's history. However, the current definition of cataplexy is not very precise and the common distinction between “typical” and “atypical” cataplexy is not well codified.

Methods: We aimed to provide a detailed description of the phenotypic variability of cataplexy. We included 109 patients with a definite history of cataplexy and a proven hypocretin-1 deficiency. The questionnaire contained 37 items to broadly cover the clinical aspects of cataplexy, including triggers, pattern and duration of muscle weakness, associated aspects such as sensory phenomena, and limitations in daily life due to cataplexy.

Results: “Laughing” only listed in place 11th of most frequent triggers. “Laughing excitedly” was much more potent, showing that a certain intensity of the emotion is important for a “cataplectogenic” effect. Anger was the highest ranking “non-humorous” trigger, followed by “unexpectedly meeting someone well known.” About 60% of patients also had spontaneous cataplectic attacks. Forty-five percent of patients experienced both partial and complete attacks and 30% only partial cataplexy. Fifteen percent of complete attacks were reported to last longer than 2 min. An abrupt return of muscle function was an important feature. The jaw and the face were most often involved in partial attacks, even more than the knee or the leg.

Conclusions: Cataplexy presents with a large phenotypical diversity, so the current “typical” versus “atypical” distinction may be difficult to hold. We propose that grading cataplexy with different levels of diagnostic confidence may be more useful.

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1. Introduction

Narcolepsy often goes unrecognized; for patients suffering from narcolepsy with cataplexy, the average time between symptom onset and final diagnosis is more than 10 years [1]. As narcolepsy typically manifests around adolescence, the diagnostic delay may have a severe detrimental effect on education, personal and social development and career opportunities [2]. The reason narcolepsy is often not recognized or accurately diagnosed may be related to the fact that the central symptom of narcolepsy—excessive daytime sleepiness—is rather nonspecific and frequently regarded as secondary to insufficient sleep by physicians. In contrast, cataplexy, the

other core symptom and virtually 100% specific, is much more difficult to diagnose [3].

In the current International Classification of Sleep Disorders (ICSD-2) cataplexy is defined descriptively as “sudden and transient episodes of loss of muscle tone triggered by emotions” [4]. In addition, “episodes must be triggered by strong emotions—most reliably laughing or joking—and must be generally bilateral and brief (less than two minutes).” In practice, this definition can be difficult to apply. For one, this is due to the fact that the cataplexy phenotype differs widely in narcoleptic patients. It may range from a few partial attacks triggered by hearty laughter per year, to several attacks per day with varying involvement of muscle groups and triggered by a range of emotions [5]. Second, feelings of muscle weakness when laughing out loud are regularly reported in the general, healthy population as well [6].

In the ICSD-2 description of narcolepsy *without* cataplexy, it is mentioned that “doubtful or atypical cataplexy-like episodes may

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be reported" [4]. This implicates that there is also such an entity as "typical cataplexy" and that a distinction with atypical cataplexy should be made. This separation is made more often in the literature, although in practice it is very troublesome. While typical cataplexy is codified to some extent, atypical cataplexy lacks a clear definition and covers a range of phenomena: from classical narcolepsy, to muscle weakness due to other causes, to the benign phenomena of being "weak with laughter" in otherwise healthy subjects.

The discovery of defects in hypocretin signaling as the central pathophysiology of narcolepsy quickly resulted in the development of a new diagnostic instrument [7]. It is now clear that the vast majority of patients with narcolepsy with cataplexy lack hypocretin-1 in the cerebrospinal fluid (CSF). The group of hypocretin-1 deficient narcoleptics is more homogenous than narcolepsy patients with normal hypocretin levels [7]. This holds not only true for the presence of "typical" cataplexy, but also for other disease markers such as HLA DQB1*0602. The available data suggest that cataplexy is strongly associated with hypocretin-1 deficiency [7–9]. In prospective clinical studies, about 90% of patients with "typical" cataplexy are hypocretin deficient [10]. In patients without cataplexy, or with an atypical phenotype, the percentage of hypocretin deficiency is much lower. On the other hand, a very small number of patients with clinically unequivocal narcolepsy with cataplexy turn out to have normal hypocretin levels [7,8,11].

Several studies have described the clinical phenotype of cataplexy, mainly based on questionnaire data [5,12–15]. Up until now, this has not been done in a large cohort of patients with known hypocretin-1 status. As hypocretin-1 deficiency defines the most homogenous and typical subgroup of narcoleptics, hypocretin deficiency should serve as the diagnostic gold standard when defining the essential aspects of the cataplexy phenotype. In the present study, we aimed to provide a broad description of the phenotypic variability of cataplexy. We studied a large cohort of patients, in all of whom the presence of cataplexy was individually confirmed by a narcolepsy-expert and hypocretin-1 levels were available.

2. Methods

2.1. Patients

We broadly approached the narcolepsy patients in two large sleep medicine centers (Leiden and Heeze). All patients were diagnosed with narcolepsy with cataplexy and fulfilled the diagnostic criteria of the second edition of the International Classification of Sleep Disorders [4]. Importantly, we only approached patients with a definite history of cataplexy, as determined by a narcolepsy-expert (G.J.L. or S.O.). In addition, we only included patients in whom CSF hypocretin-1 levels were available. Hypocretin-1 measurements were done according to previously reported methods [16], using a reference sample to enable comparison with published diagnostic values [7].

Questionnaires were given to the patients during a clinical visit, or by mail. Filled-out questionnaires could be returned using an included stamped envelope. Subjects did not receive compensation for their participation in the study. The study was exempted from review by the Ethical Committees of the participating hospitals.

2.2. Questionnaire

A questionnaire was designed to broadly cover the clinical aspects of cataplexy. Note that the questionnaire was not designed as a diagnostic tool. The final survey contained 37 items. Patients using medication were asked to fill-out the questionnaire to de-

scribe the situation at the time they were not medicated. Patients first described in their own words the triggers and patterns of their "typical attack," with a narrative description of such an event. The majority of other items were multiple-choice questions, with free-text space to provide optional additional comments. The questions broadly covered three main themes. First, we inquired in detail about the triggers for cataplexy for a wide range of emotions/situations. To enable a descriptive analysis, we opted to probe a range of specific emotions. The list was put together based on the existing literature and supplemented with various triggers that we have encountered in our clinical practice, where the phenotype of cataplexy receives particular attention. Second, the pattern of muscle weakness was explored, including the involved muscle groups. "Complete attacks" were defined when the patient perceived (virtually) all muscles of the body to be involved. "Partial attacks" were defined as attacks in which distinct parts of the body were affected, with normal muscle function in other parts. Duration of attacks was rated in seven discrete categories, ranging from <2 s to >15 min. Third, we asked about associated aspects such as sensory phenomena, as well as consequences such as injury. This part also included a description of the type of treatment and the effect this had. Furthermore, we explored the limitations that patients experience in daily life due to cataplexy.

2.3. Analyses

Descriptive statistics were performed using the SPSS for Windows package (V 14). Data were either presented as n (%), or mean \pm standard deviation (SD). Per item, less than 10% of answers could not be used (missing data, more than one answer given, etc.). Because of this low rate, we decided to present valid percentages throughout the paper (i.e., the percentage of positive answers compared to the number of complete answers given). Items were compared between males and females using Chi-square statistics or t -tests where appropriate.

3. Results

3.1. Participants

Analyzable questionnaires were available in 116 patients. Of this group, 109 patients (94%) had undetectable CSF hypocretin-1 levels (60 males, mean age 42.6 ± 15.5 years, age range 16–79 years), confirming the strong association between cataplexy and hypocretin-1 deficiency. In Table 1, demographic data are listed. In the whole group, the average age was 42 years, with 52% of males. Disease duration at the time of study was a little over 15 years. Interestingly, only half of the patients used medication for cataplexy. Hypocretin deficient patients had about one attack per day on average (Table 1), at least when partial attacks are concerned. Complete attacks occurred less frequently (on average 8.4 attacks per month). Attack frequency, duration and trigger profile did not differ between males and females.

Although the small number of subjects precluded meaningful statistics, patients with normal hypocretin level had a noticeable lower attack frequency and a younger age at onset (Table 1). However, there were no striking differences in other cataplexy features between patients with and without hypocretin deficiency, and we therefore only describe the hypocretin deficient patients in the rest of the results.

3.2. Cataplexy triggers

In Fig. 1, the various triggers for cataplexy are shown. We sorted the triggers in descending order, based on the percentage of

Table 1
Demographic and clinical data.

	All	Hypocretin-1 deficient	Hypocretin-1 normal
N	116	109	7
Age (years)	41.8 ± 15.4	42.6 ± 15.5	29.3 ± 4.5
Males (%)	60 (51.7%)	59 (54.1%)	1(14.3%)
Age at onset (years)	25.8 ± 12.4	26.5 ± 12.3	13.5 ± 6.8
<15	19 (16.4%)	17 (16.0%)	2 (33.3%)
15–25	43 (37.1%)	39 (36.8%)	4 (66.7%)
>25	50 (43.1%)	50 (47.2%)	0
Disease duration (years)	15.6 ± 13.3	15.4 ± 13.8	15.7 ± 10.1
Cataplexy frequency (attacks/month)			
Total	37.6 ± 100.1	39.4 ± 102.9	10.5 ± 21.9
Partial	29.2 ± 83.2	30.5 ± 85.6	9.8 ± 22.2
Complete	8.4 ± 24.1	8.9 ± 24.8	0.8 ± 1.5
Using medication (%)	65 (56.0%)	64 (58.7%)	1 (14.3%)

Age at onset: appearance of the first symptom later attributed to narcolepsy. Frequency data are shown as valid percentages.

patients that answered “often” or “always.” Although “laughing” is considered the most important trigger for cataplexy, it only listed in 11th place. Apparently, other qualities need to be associated with laughter to reliably evoke cataplexy. The top six triggers are indeed all associated with laughing or humour, with “laughing excitedly” as the most frequent trigger. When patients tell a joke themselves, this more often resulted in cataplexy than hearing someone else tell a joke. Likewise, making a sharp, witty remark was a very strong trigger.

Anger was the highest ranking “non-humorous” trigger, although 30% of patients never reported cataplexy when being angry. Unexpectedly meeting someone well known was another frequently experienced trigger. This was mentioned by Daniels in his

1934 landmark monograph, but very seldom afterwards [17]. Here, the intensity of the emotion again seemed important, in addition to some form of surprise: *expectedly* meeting someone well known or meeting just an acquaintance resulted in cataplexy much less often. Being startled was the third non-humorous emotion listed in the top 10 triggers.

Although mentioned as the “prototypical” trigger throughout the literature, plain “laughing” never evoked cataplexy in 32 patients (29%). To assess whether these patients have a different “trigger profile,” we plotted trigger frequencies in these patients (Fig. 2). In this group, “laughing excitedly” triggered cataplexy in the majority of patients, so it is important to always inquire specifically about this type of laughing. In addition, making a sharp minded remark or telling a joke evoked cataplexy in the majority, indicating that *mirth*, the emotion associated with laughter, is in fact the triggering factor. Another noteworthy finding was that experiencing cataplexy during an orgasm was reported relatively often in patients in whom laughing does not reliably trigger cataplexy. The term “orgasmolepsy” has been proposed by others [18].

Only eight patients reported that even laughing excitedly never triggered their cataplexy. Although very rare, it underscores the importance of inquiring about other emotions, because joking, being angry and unexpected meetings were reported as important triggers in these patients.

Although not very frequent, about 60% of patients recognized spontaneous cataplectic attacks, without an identifiable trigger. Physical exercise was sometimes reported by patients to evoke cataplexy. However, it is difficult to ascertain whether this constitutes the exercise itself, or an emotion associated with it (e.g., realizing the perfect opportunity to deliver a win in tennis). When asked about exercise, 50.5% of patients indicated this possibility. When exercise was reported, 58.8% of patients recognized a clear emotion to be associated with the event.

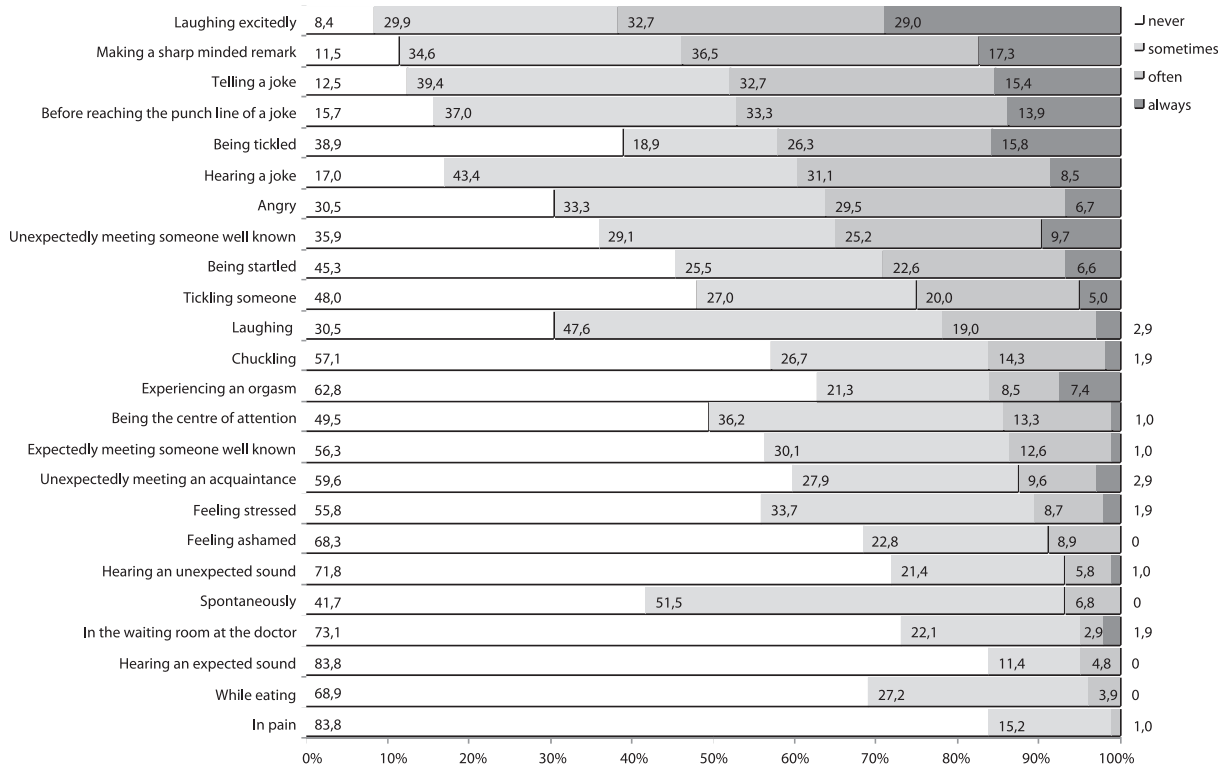


Fig. 1. Cataplexy triggers in patients with hypocretin-1 deficiency (n = 109). The triggers are sorted in descending order, based on the frequency of answers scored as ‘often’ or ‘always’.

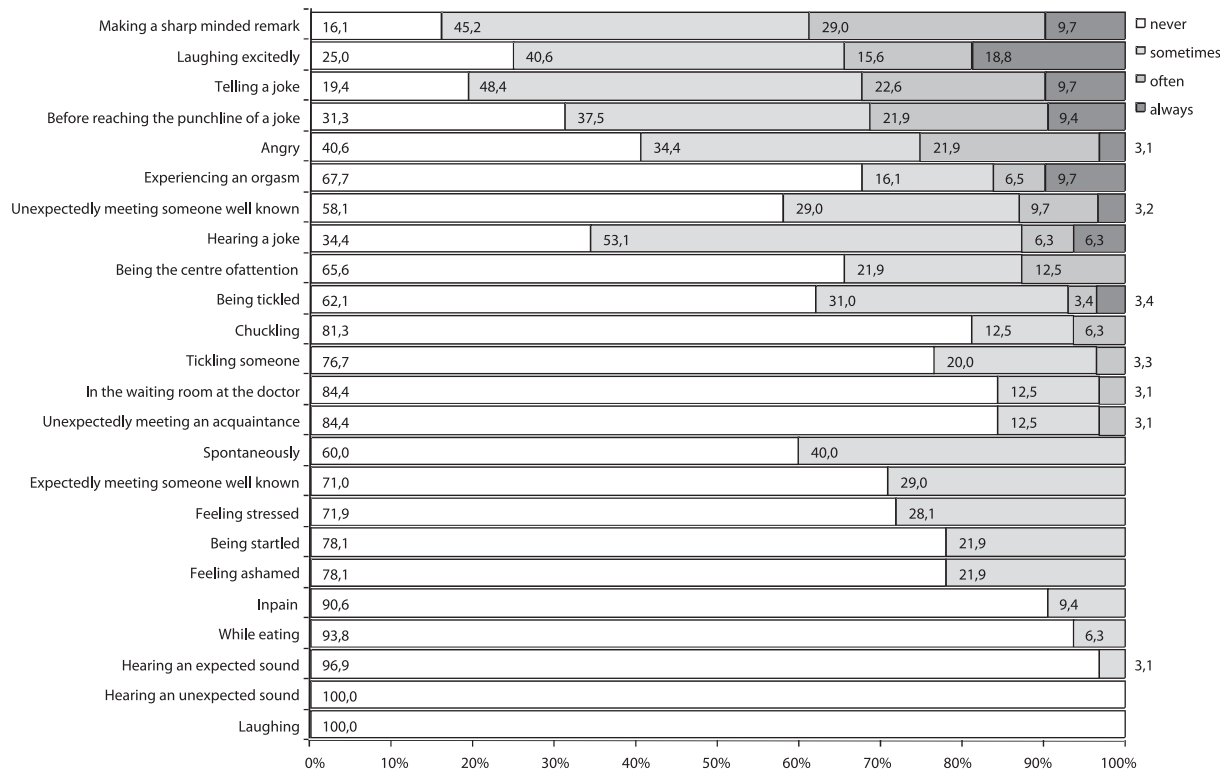


Fig. 2. Frequency of cataplexy triggers in those patients who reported never to have cataplexy in response to plain 'laughing' ($n = 32$). The triggers are sorted in descending order, based on the frequency of answers scored as 'often' or 'always'.

3.3. Patterns of muscle weakness

Forty-five percent of the patients experienced both partial and complete cataplectic attacks (Table 2). Almost 30% reported having only partial attacks, and 24% only complete attacks. This underscores the importance to always separately inquire about the presence of partial and complete attacks.

Although most attacks were short, 15% of complete cataplectic attacks were reported to last longer than 2 min (Fig. 3). However, partial attacks were typically very short, lasting less than 10 s. The duration of complete attacks was more variable, including attacks lasting several minutes. Importantly, when specifically questioned about long lasting complete attacks, only 28% of patients reported this to be one single episode. Most complete attacks lasting longer than 5 min were composed of consecutive shorter attacks. In addition, many patients reported that these instances were associated with a continuing trigger (for example, when friends kept joking).

An abrupt return of muscle function was an important feature. Almost 90% of patients reported that they had normal muscle function immediately after a cataplectic attack.

Only a minority of patients (16.5%) reported unilateral cataplexy. In many cases, review of the narrative description of a typical attack revealed that the attacks were bilateral, but one side of the body was perceived as distinctly more affected. All skeletal muscle groups could be involved in cataplexy (Table 2). The jaw and the face were most frequently affected, even more than the knee or the leg. This is important, as a feeling of muscle weakness in the lower limbs caused by laughing is quite a normal phenomenon in the normal population. The neck muscles were also frequently involved, resulting in drooping of the head. More than half of patients reported cataplexy to be associated with "jerks" and twitches in various parts of the body, including the face and arms.

Table 2
Cataplexy phenotype.

	Hypocretin-1 deficient ($n = 109$)
Pattern of muscle weakness	
Type of attacks:	
Only complete	25 (23.8%)
Only partial	31 (29.5%)
Both partial & complete	49 (45.7%)
Duration of complete attacks	
<30 s	45 (61.6%)
<2 min	63 (86.3%)
Complete attacks >5 min	
Single, long attack	14 (28.0%)
Consecutive short attacks	23 (46.0%)
Can be both	13 (26.0%)
Duration of partial attacks	
<30 s	79 (83.2%)
<2 min	89 (93.7%)
Muscles can be used immediately after attack	95 (89.6%)
Self-perceived unilateral paralysis	17 (16.5%)
Muscle groups involved	
Knee, leg	67 (67.7%)
Neck, head	57 (57.6%)
Jaw, face	69 (69.7%)
Shoulder	17 (17.2%)
Arm	35 (35.4%)
Hand	46 (46.5%)
Muscles related to speech	43 (43.4%)
Other	8 (8.1%)
Muscle twitches during cataplexy	57 (54.3%)
Consciousness	
Conscious at the beginning of an attack	109 (100%)
Hallucinations during cataplexy	29 (26.6%)
If yes:	
At the beginning of an attack	16 (35.0%)
Half way	27 (60.0%)
Towards the end	2 (6.7%)

Frequency data are shown as valid percentages.

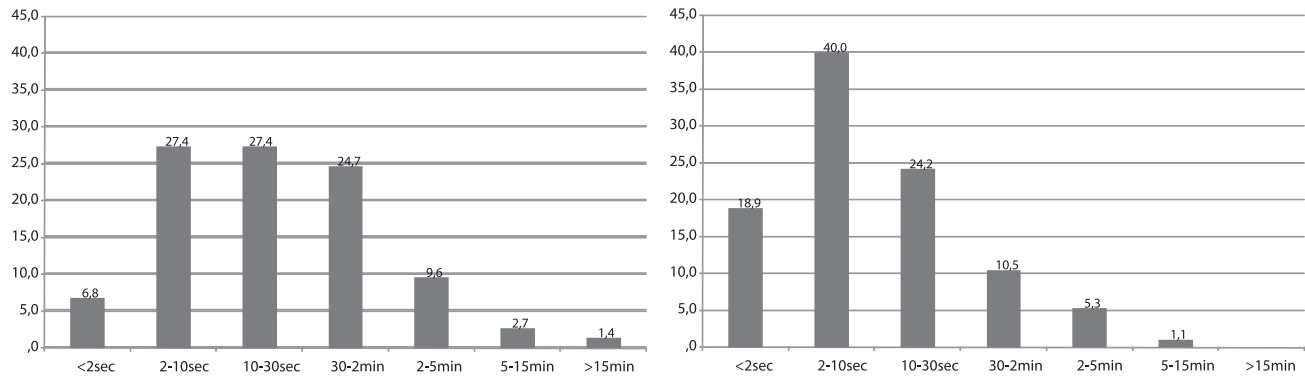


Fig. 3. Mean duration of cataplectic attacks in hypocretin-1 deficient patients ($n = 109$). Histograms reporting the frequency of different duration categories for complete cataplexy (left) as well as partial attacks (right).

Interestingly, more than a quarter of patients reported the occurrence of hallucinations during cataplexy, most of the time halfway or at the end of an episode. This raises the question whether hallucinations can occur in the context of cataplexy itself or whether sleep episodes may also occur during cataplexy, especially during longer attacks. At least in the beginning of the attack, all patients reported to be awake.

3.4. Warning signs and tricks to prevent cataplexy

About 57% of patients could feel a cataplexy attack coming, making it possible to take countermeasures, such as sitting down (Table 3). These warning signs were not only composed of commencing partial muscle weakness; 48% reported having a “strange feeling in the head” just before the cataplexy started. Almost 60% of patients developed certain tricks to try and prevent a cataplectic attack to occur or to influence the severity or duration of an attack; examples included “trying to think of something else,” “putting tension on my muscles,” or “pressing against a firm support surface.” Indeed, 42% of patients had the impression that trying hard to resist an attack resulted in a shortening of the episode. However, in 18%, this resistance actually made an attack last longer. This

Table 3
Additional cataplexy aspects.

	Hypocretin-1 deficient ($n = 109$)
Warnings	
Can feel an attack coming	61 (57.0%)
‘Strange feeling in the head’ before an attack	50 (48.5%)
Has tricks to prevent an attack	63 (58.3%)
Can ‘resist’ an attack when it starts	49 (46.2%)
When resisting, the attack lasts shorter	24 (42.9%)
When resisting, the attacks lasts longer	10 (17.9%)
Resisting changes which body parts get weak	25 (24%)
Finding support prolongs the attack	25 (24%)
Presence of ‘bad days’, with more cataplexy	43 (40.6%)
More cataplexy when tired	82 (76.6%)
Consequences	
In case of falling	
Falls straight down	25 (33.3%)
Falls to the floor within 5 s	43 (58.1%)
Injury due to cataplexy	
Never	60 (56.6%)
Seldom	31 (29.2%)
Sometimes	11 (10.4%)
Often	4 (3.8%)

Frequency data are shown as valid percentages.

was even clearer in the case of finding support to prevent a complete attack. A quarter of patients reported this to prolong the attack, and many patients said that only when they finally let go, the attack became complete but subsided quickly.

Forty percent of patients recognized the presence of “bad days,” certain days in which the frequency of cataplexy was higher (Table 3). Often, there was no specific reason for this increase in cataplexy frequency. Some patients reported that when they get up from bed in the morning, they already have a feeling it will be one of those days with frequent attacks. In general, “tiredness” was reported to be associated with more frequent cataplexy.

3.5. Consequences of cataplexy

When cataplexy is complete, and occurring in a standing patient, this may lead to falls. One-third of patients reported to fall straight down during complete attacks. Falls towards the left or the right (17.9%) and forward falls (13.4%) occurred less frequently. The remainder of the patients did not report a fixed direction of their falls. In patients with falls due to cataplexy, 58% reported to fall to the floor very quickly, within 5 s.

Usually, it is assumed that cataplexy does not lead to injury often. However, when assessed retrospectively, almost half of patients have sustained some form of injury at one point in time (Table 3). Fourteen percent reported to injure themselves due to cataplexy on a regular basis. The most common injuries were bruises and excoriations of the limbs. But 22 patients (20.2%) had experienced at least one severe injury due to cataplexy. In 17 of these, the head was involved, ranging from superficial wounds, dental damage or even a concussion. Without specific inquiry, eight patients reported dangerous situations in which they had experienced cataplexy, such as working on a roof top, standing on a ladder, or during biking. Three patients even reported a near-drowning experience, due to cataplexy while swimming.

3.6. Limitations in daily life

In Table 4, the limitations in daily life are listed that are caused by cataplexy. One-third of patients reported strong limitations in daily activities, evident in all different aspects of daily life, in comparable degrees.

3.7. Treatment effect

Fifty-six percent of patients used medication for cataplexy, either antidepressants or sodium oxybate. Virtually everyone (97.9%) reported a clear beneficial effect of the medication on cataplexy. The strongest effect of medication was lower frequency of

Table 4
Extent of limitations due to cataplexy.

	No/slight		Moderate		Strong/very strong	
	n	%	n	%	n	%
Daily activities	70	69.3	19	18.8	12	11.9
Family life	64	62.1	20	19.4	19	18.4
Recreation	54	52.4	23	22.3	26	25.2
Education/employment	49	49.0	16	16.0	35	35.0
Driving a car	61	66.3	6	6.5	25	27.2

n = 109, hypocretin-1 deficient. Frequency data are shown as valid percentages.

cataplexy (mentioned by 86.4% of patients). Only 12.5% of patients reported an influence of medication on the severity of cataplexy, i.e., on the number of muscles involved, or “changing” complete attacks into partial ones. Behavioural changes led to less attacks in 27.1% (for instance, living a steady lifestyle and avoiding sleep deprivation).

4. Discussion

In this study, we provide a clinical description of cataplexy in the largest cohort of narcolepsy patients with cataplexy so far. In addition, hypocretin levels were known in all patients, making it possible to describe the cataplexy phenotype in the homogenous group of hypocretin deficient patients. We confirmed essential aspects such as preserved consciousness—at least at the beginning of attacks—and short duration, although complete cataplexy quite regularly lasted longer than 2 min. We show that an abrupt return of muscle function is an important feature of cataplexy. While laughing is thought to be the prototypical trigger for cataplexy, the emotional trigger needs to have other qualities, such as a sufficient intensity or unexpectedness. Besides laughter, there are other important—unrelated—triggers, such as anger, startle and unexpected meetings. Although we probed an extensive list of possible triggers, there may be others that were not included. The narrative descriptions in our cohort did not yield other situations, but future studies should always include the possibility for patients to add additional triggers. Although most attacks do not result in injury, the life-time prevalence of injury due to cataplexy is about 50%. Furthermore, the presence of cataplexy poses severe limitations in daily life in many patients.

When looking at cohorts of narcolepsy patients, the “typical” features of cataplexy emerge which are mentioned above. Nonetheless, cataplexy remains a difficult symptom to confidently diagnose in daily practice. Many patients have what is currently called “atypical” cataplexy, although this identity is poorly codified. In part, this difficulty may stem from the fact that laughter is the trigger with the highest sensitivity, but also the lowest specificity, as many healthy people do experience some form of muscle weakness when laughing out loud [6,13]. In this regard, it is clinically important to try and identify other types of triggers in every patient. In fact, in future studies it will be useful to always screen the most important triggers in every patient, including intense laughing, making a witty remark and telling a joke. In addition, anger, startle and unexpected meetings should be separately scored. A prospective diagnostic study can then assess the effects on diagnostic “performance,” for example, using the criterion of at least two different triggers to diagnose cataplexy.

The same reasoning holds true for the pattern of muscle weakness. “Being weak with laughter” in the general population most often concerns the lower limbs [6]. For cataplexy, weakness of the neck (resulting in head drops), the face and jaw and slurred speech are very typical and likely to be more specific [13–15].

Future diagnostic studies should separately assess the involvement of these muscle groups in every patient.

In clinical practice, the physician seeks to identify as many different aspects of the presumed cataplectic attacks as possible. The combination of symptoms determines whether the final diagnosis is indeed “cataplexy.” The more features are present, the higher the confidence level to make a diagnosis. Nowadays, finding an undetectable hypocretin-1 concentration in the CSF makes it even more likely that suspected attacks of muscle weakness are indeed cataplexy. In this regard, diagnosing cataplexy using different levels of diagnostic confidence may be more useful than the current “typical” versus “atypical” distinction. One could classify cataplexy as “definite,” “probably” or “possible,” depending on the presence or absence of a number of key features, such as triggers, pattern of muscle weakness, and duration. Although hypocretin measurements do not directly measure the presence of cataplexy, the tight link between cataplexy and undetectable hypocretin-1 levels in the CSF suggest that a “laboratory supported” diagnosis of cataplexy is also a useful concept. This diagnostic system would not only be useful in clinical practice, but also for research studies. Especially in genetic association studies it is of crucial importance to have a clear and confident diagnostic classification.

Descriptive studies in larger patient populations are only possible in people who already have a confident diagnosis of cataplexy [14,19]. Often, these patients are treated already, and to very good effect, as we have shown here as well. We therefore chose to ask patients to describe their cataplexy “retrospectively” during the time they did not have medication. However, this makes it difficult to study influencing factors such as age, severity, and duration of symptoms. A prospective study including untreated patients in the diagnostic phase will be able to address this question. Such a study should use a validated diagnostic questionnaire and could also probe the potential of a graded diagnostic system as described above. This will only be feasible in a multi-center setting across different countries.

Many interesting topics remain to be explored in future studies, such as the change of cataplexy phenotype with age. It is well known that cataplexy frequency may decrease over the years, but character and severity may as well. Finally, the wide variability in cataplexy expression raises the question whether there may be differences in the pathophysiological mechanisms involved.

Conflicts of interest

All authors confirm that there is no financial support from or other involvement with organizations with financial interest in the subject matter of this paper.

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