Delayed Diagnosis, Range of Severity, and Multiple Sleep Comorbidities: A Clinical and Polysomnographic Analysis of 100 Patients of the Innsbruck Narcolepsy Cohort

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Study Objectives: Narcolepsy is reported to affect 26-56/100,000 in the general population. We aimed to describe clinical and polysomnographic features of a large narcolepsy cohort in order to comprehensively characterize the narcoleptic spectrum.

Methods: We performed a chart- and polysomnography-based review of all narcolepsy patients of the Innsbruck narcolepsy cohort.

Results: A total of 100 consecutive narcolepsy patients (87 with cataplexy [NC], 13 without cataplexy [N]) were included in the analysis. All subjects had either excessive daytime sleepiness or cataplexy as their initial presenting clinical feature. Age at symptom onset was 20 (6-69) years. Diagnostic delay was 6.5 (0-39) years. The complete narcolepsy tetrad was present in 36/100 patients; 28/100 patients had three cardinal symptoms; 29/100 had two; and 7/100 had only excessive daytime sleepiness. Severity varied broadly with respect to excessive daytime sleepiness (median Epworth Sleepiness Scale score: 18, range 10-24), cataplexy (8-point Likert scale: median 4.5, range 1-8), hypnagogic hallucinations (median 4.5, range 1-7), and sleep paralysis (median 3, range 1-7). Sleep comorbidity was highly prevalent and ranged from sleep-related movement disorders ($n = 55/100$), parasomnias ($n = 34/100$), and sleep-related breathing disorders ($n = 24/100$), to insomnia ($n = 28/100$). REM sleep without atonia or a periodic limb

movement in sleep index $> 5/h$ were present in most patients (90/100 and 75/100). A high percentage of narcoleptic patients in the present study had high frequency leg movements (35%) and excessive fragmentary myoclonus (22%). Of the narcolepsy patients with clinical features of REM sleep behavior disorder (RBD), 76.5% had EMG evidence for RBD on the multiple sleep latency test (MSLT), based on a standard cutoff of a minimum of 18% of 3-sec mini-epochs.

Conclusion: This study is one of the largest monocentric polysomnographic studies to date of patients with narcolepsy and confirms the frequent comorbidity of narcolepsy with many other sleep disorders. Our study is the first to evaluate the percentage of patients with high frequency leg movements and excessive fragmentary myoclonus in narcolepsy and is the first to demonstrate EMG evidence of RBD in the MSLT. These findings add to the growing body of literature suggesting that motor instability is a key feature of narcolepsy.

Keywords: Polysomnography, cohort, diagnosis, hypersomnia, hypocretin, sleep paralysis, gender

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Narcolepsy is a chronic neurological disorder with a reported prevalence of 0.026 to 0.056 % in the general adult population,^{1,2} although it has been suggested that up to 2.3% of subjects in the general population fulfill diagnostic criteria for narcolepsy.³ There is ongoing evidence that hypocretin deficiency results from an autoimmune attack on hypocretin cells, and recent genetic findings underline the importance of antigen presentation by HLA class II to T cells in its pathophysiology.⁴

Cardinal features of narcolepsy are excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep.⁵ According to cataplexy status, two main categories of narcolepsy are differentiated.⁵ A diagnosis of narcolepsy with cataplexy requires polysomnography demonstrating a sleep latency < 8 minutes plus ≥ 2 sleep onset REM episodes in the multiple sleep latency test (MSLT), or alternatively assessment of hypocretin-1 levels in the cerebrospinal fluid ≤ 110 pg/mL.⁵

BRIEF SUMMARY

Current Knowledge/Study Rationale: Studies on large, well defined series of narcolepsy patients have focused primarily on clinical features of narcolepsy. In contrast, there is paucity of data concerning thoroughly documented polysomnographic comorbidity in large narcolepsy patient samples.

Study Impact: This study is the largest monocentric polysomnographic series to date of patients with narcolepsy with a special emphasis on motor phenomena during sleep. Presence of REM sleep without atonia, a periodic leg movement in sleep index $> 5/h$, and sleep fragmentation can be regarded as further polysomnographic hallmarks of the disease, whereas insomnia does not speak against a diagnosis of narcolepsy.

Studies on large, well-defined series of narcolepsy patients have focused primarily on clinical features of narcolepsy,⁶⁻⁸ while there is paucity of data concerning thoroughly documented polysomnographic comorbidity in large narcolepsy patient samples.^{9,10}

In this light, we aimed to thoroughly describe the entity of narcolepsy concerning both clinical and polysomnographic characteristics with a special focus on sleep-related movement disorders, based on a large tertiary-referral cohort with definite narcolepsy.

METHODS

Setting

The Innsbruck sleep laboratory is a tertiary sleep disorder referral center serving a population of about 2 million. It is the only academic facility for diagnosis and treatment of sleep disorders in Western Austria and South Tyrol (Northern Italy), but serves patients from other parts of Austria as well. Patients represent the full spectrum of sleep disorders according to major categories of the second edition of the International Classification of Sleep Disorders (ICSD-2).⁵

All patients who were entered into our clinical database since 1998 and met the diagnostic criteria for narcolepsy according to ICSD-2 criteria were included in this study. All subjects had either excessive daytime sleepiness or cataplexy as their initial presenting clinical feature. In addition to a comprehensive sleep history, all patients underwent HLA testing and polysomnographic workup. MSLT was done in all patients admitted for diagnostic evaluation or re-evaluation of narcolepsy. In a minority of patients ($n = 13$) who were diagnosed at external sleep centers and had an unambiguous history of cataplexy ($n = 13$), positive MSLT testing ($n = 13$), or positive cerebrospinal fluid hypocretin-1 results ($n = 1$), MSLT was either not repeated ($n = 5$) or repeated while maintaining preexisting medication (7 antidepressants, 1 sodium oxybate). Assessment of cerebrospinal fluid concentrations were performed only when needed for diagnostic purposes according to the guidelines of the European Federation of Neurological Societies for cerebrospinal fluid investigations.¹¹

Chart and Polysomnographic Review

For this study, all consecutive narcolepsy patients of the Innsbruck narcolepsy database were selected. The database included information on demographics (age, gender, body mass index), narcolepsy-specific clinical information (age at disease onset, age at diagnosis, presence and severity of daytime sleepiness, cataplexy, sleep paralysis, or hypnagogic hallucinations), information on narcolepsy workup (HLA typing, MSLT, hypocretin-1 measurements when needed for a diagnosis), as well as sleep comorbidities according to ICSD-2 categories (insomnia, sleep-related breathing disorders, parasomnias, sleep-related movement disorders).⁵ Severity of daytime sleepiness was assessed by the Epworth Sleepiness Scale score¹²; severity of cataplexy, sleep paralysis, and hypnagogic hallucinations was scored on an 8-point Likert scale ranging from 1 (referring to rare and mild symptoms) to 8 (referring to very frequent and severe symptoms) as used for the genetic collaboration with the Stanford Center for Narcolepsy.¹³ Body mass index (BMI) percentiles of narcolepsy patients were compared to BMI percentiles obtained from the general population.¹⁴ In addition, we reviewed the polysomnographic recordings of all patients to determine the presence or absence of sleep-related motor phe-

nomena such as REM sleep without atonia,⁵ periodic leg movement in sleep index $> 5/h$,¹⁵ high frequency leg movements (alternative terms: hypnagogic foot tremor and alternating leg muscle activation during sleep),¹⁶ excessive fragmentary myoclonus,¹⁷ and bruxism.¹⁸ The presence or absence of REM sleep without atonia during polysomnography was rated in line with the current ICSD-2 criteria.⁵ No quantitative scoring of EMG activity during REM sleep was performed.¹⁹

In order to answer the question as to whether EMG features of REM sleep behavior disorder (RBD) in narcolepsy are apparent during the MSLT, REM sleep-related EMG activity in the mentalis muscle was quantified during the MSLT in the group of narcolepsy patients with RBD.¹⁹ For the MSLT, every 30-sec epoch was divided into ten 3-second mini-epochs. The percentage of mini-epochs with “any” EMG activity was divided by the total number of mini-epochs.¹⁹ Motor events during sleep in the MSLT were assessed with the RBD severity scale.²⁰ These polysomnographic data were added to the existing database for further analyses.

The establishment of a narcolepsy database was approved by the local ethics committee of Innsbruck Medical University, and all patients gave written informed consent.

Statistics

SPSS for Macintosh, version 19.0 was used for data analysis. Normality was tested by using the Shapiro-Wilks test. All values are presented as means $\pm$ standard deviation in the case of normal distributions, or as medians (range) in the case of non-normal distributions. For assessing associations between narcolepsy subtype narcolepsy-cataplexy (NC) or narcolepsy without cataplexy (N), gender, and clinical as well as polysomnographic correlates, nonparametric statistics (χ^2 tests and Mann-Whitney U tests) were performed. For correlation analysis, a Spearman correlation coefficient was calculated. P-values < 0.05 were considered to indicate statistical significance.

RESULTS

Characterization of the Innsbruck Narcolepsy Cohort

As of May 2012, 100 patients (56 men, 44 women) with established narcolepsy were registered in our sleep centre's clinical database. The median age was 39 (range 16-78) years. The median age at symptom onset was 21 (6-69) years. The median Epworth sleepiness score at time of diagnosis was 18 (10-24). The majority of cases had NC (87%); 13% of patients had N. The severity of cataplexy varied markedly (median 4.5 [range 1-8]) on an 8-point Likert scale. Additional cardinal features were sleep-related hallucinations in 56% of patients and sleep paralysis in 50% of patients. For severity of sleep-related hallucinations and sleep paralysis see **Table 1**. The complete narcolepsy tetrad was present in 36% of cases; 28% of patients had 3 cardinal symptoms; 29% had two cardinal symptoms; and 7% had only excessive daytime sleepiness. The median body mass index of the total group was 26.2 (18.2-43.0) kg/m². Twenty-three percent of patients (12 men, 11 women) had a BMI > 30 kg/m². More narcolepsy patients than expected were found for BMI percentiles > 50 (60 observed compared to 50 expected) and > 90 (14 observed compared to 10 expected). Sleep paraly-

Table 1—Demographic and clinical characteristics of narcolepsy patients

	Total group (n = 100)	NC (n = 87)	N (n = 13)	p-value (NC vs. N)
Men, n/total	56/100	49/87	7/13	1.000
Body mass index	26.2 (18.2-43.0)	26.3 (18.2-43.0)	23.8 (20.1-31.6)	0.125
Epworth sleepiness score	18 (10-24)	18 (10-24)	16 (13-21)	0.052
Sleep paralysis, n/total	50/100	46/87	4/13	0.234
Hypnagogic hallucinations, n/total	56/100	51/87	5/13	0.233
Sleep paralysis, severity	3 (1-7)	3 (1-7)	1 (1-4)	0.076
Hypnagogic hallucinations, severity	4.5 (1-7)	5 (1-7)	2 (1-3)	0.021
Interval to diagnosis, years	6.5 (0-39)	7 (0-39)	6 (2-26)	0.930

NC, narcolepsy with cataplexy; N, narcolepsy without cataplexy.

sis, sleep-related hallucinations, as well as daytime sleepiness indicated by the Epworth score tended to be more severe in NC than N patients. No other variables differed between both groups (see **Table 1**). Concerning gender, women had higher Epworth scores than men (19 [10-23] vs. 17 [11-24], $p = 0.038$). The following features did not differ between male and female narcolepsy patients: presence and severity of cataplexy (presence women vs. men: 38/44 vs. 49/56, severity: 5 [2-7] vs. 5 [3-8]), sleep paralysis (presence: 25/44 vs. 25/56, severity: 3 [1-7] vs. 4 [2-6]), hypnagogic hallucinations (presence: 28/44 vs. 28/56, severity: 5 [1-7] vs. 4 [3-7]), age at first symptoms (21.5 [12-69] vs. 20 [6-54] years), interval between first symptoms and diagnosis (8.5 [0-39] vs. 5 [0-36] years), and BMI (25.2 [18.2-43] vs. 26.4 [20.1-33.8], all $ps > 0.05$).

Diagnostic Workup Data

All patients underwent HLA typing for DQB1*0602 and DRB1*1501. HLADQA1*0102 was assessed in 48 cases. Ninety-three percent of patients were HLA DQB1*0602 positive; 92% were DRB1*1501 positive; and 44 (92%) were DQA1*0102 positive. All patients but one who were DQB1*0602 positive were also positive for DRB1*1501. DQB1*0602 and DRB1*1501 but not DQA1*0102 differed according to cataplexy status (NC vs. N: DQB1*0602: 85/87 vs. 8/13, $p < 0.001$; DRB1*1501: 84/87 vs. 8/13, $p = 0.001$; DQA1*0102: 39/41 vs. 5/7, $p = 0.096$).

Ninety-five patients (87 untreated, 8 treated [7 antidepressants, 1 sodium oxybate]) underwent a MSLT after a night of polysomnography. In the combined group of treated and untreated narcolepsy patients, the median sleep latency on the MSLT was 2.5 (0.1-11.7) min and the median number of sleep onset REM episodes (SOREMs) was 4 (0-5).

In the untreated group, the median sleep latency was 2.5 (0.1-11) min and the median number of SOREMs was 4 (0-5). 84 patients had 5 MSLT runs, 2 patients had 4 MSLT runs, and 1 patient had 3 MSLT runs. Four subjects from the untreated group did not fulfill polysomnographic criteria for a diagnosis of narcolepsy. Two subjects from the untreated group with definite cataplexy had a sleep latency > 8 min (9 and 11 min, respectively) with multiple SOREMs; 2 subjects from the untreated group with definite cataplexy had a short sleep latency < 8 min, with 0 and 1 SOREM, respectively. The two latter patients underwent lumbar puncture. Both had a non-detectable hypocretin-1 level in the cerebrospinal fluid.

In the treated group, the median sleep latency was 4.0 (1.2-11.7) min, and a median of 0.5 SOREMs (0-2) were detected. The MSLT sleep latency did not differ between NC and N patients (2.2 [0.1-11.0] vs. 2.9 [0.2-6.8] min; $p = 0.216$), whereas the number of SOREMs was higher in the NC group than the N group (4 [0-5] vs. 2 [2-5]; $p = 0.004$). Men and women did not differ in median MSLT sleep latency (2.5 [0.3-11] min vs. 2.5 [0.1-6.8]; $p = 0.373$) or number of SOREMs (4 [0-5] vs. 4 [2-5]; $p = 0.651$).

Eight percent of cases (all with cataplexy) underwent hypocretin-1 testing in the cerebrospinal fluid. In all 8 patients, hypocretin-1 was either undetectable ($n = 5$) or < 45 pg/mL ($n = 3$).

A maintenance of wakefulness test (MWT) was performed in 10 patients: 5 of these patients participated in the H3A trial (3 $\times$ before treatment initiation, 2 in double-blind phase), 3 patients were on methylphenidate (20, 2 $\times$ 40 mg), and 2 patients were on modafinil (200 mg, 400 mg). The median sleep latency in the MWT was 5.9 (0.5-20) min in these 10 patients.

Delayed Diagnosis of Narcolepsy and Basis for Referral

The median age at symptom onset was 20 (6-69) years. The median age at diagnosis was 32 (12-74) years. The median diagnostic delay was 6.5 (median 0-39) years (see **Figure 1**). In the majority of NC cases, excessive daytime sleepiness occurred at a median of 3 years (0.02-30) before cataplexy (55/86, 64%) or at the same time as cataplexy (27/86, 31.4%). Cataplexy was the first symptom in only 4 patients (4.7%). There was no difference in diagnostic delay in regard to either cataplexy status (cataplexy vs. non-cataplexy: 7 [0-39] vs. 6 [2-26] years, $p = 0.930$) or gender (men vs. women: 5 [0-35] vs. 8.5 [0-39] years; $p = 0.595$).

The majority of patients were referred by medical specialists ($n = 45/73$, 61.6%), predominantly neurologists ($n = 27$); 11 (15.1%) were referred via the national narcolepsy patient group; 10 (13.7%) by their general practitioner; and 7 (9.5%) referred themselves by either word-of-mouth recommendation or information obtained in the internet or media. Gender or cataplexy status did not influence the mode of referral (all $ps > 0.05$).

Medication at Last Follow-Up Consultation

Of the total sample of 100 narcolepsy cases, 67% took daily medication for narcolepsy symptoms at follow-up consultation. The majority took either wake-promoting drugs alone ($n = 29$) or in combination with anti-cataplectic medication ($n = 30$). Eight subjects took anti-cataplectic medication alone. For further de-

Figure 1—Diagnostic delay of narcolepsy diagnosis

Narcolepsy cohort

Dots represent the individual narcolepsy patients' years to diagnosis. The line represents the median diagnostic delay, which was 6.5 years (range 0-39).

tails see **Table 2**. In addition, 17% of patients took on-demand medication (16 wake-promoting medication: 13 modafinil, 3 methylphenidate; 1 clomipramine). Sixteen percent of patients took no medication at all. Cataplexy status and gender did not influence the use of wake-promoting medication (all $p > 0.05$).

Sleep Comorbidity and Additional Polysomnographic Findings

Sleep comorbidity was highly prevalent and ranged from sleep-related breathing disorders (24%), insomnia (defined as difficulty in initiating or maintaining sleep plus relevant disturbance of daytime functioning due to insomnia in addition to narcolepsy) (28%), parasomnias by history or at present (34%: 24 RBD, 10 NREM parasomnias), to sleep-related movement disorders (55%: 31 bruxism, 24 restless legs syndrome [RLS]). None of the RBD patients in this study presented at the sleep center with a main complaint of symptoms suggestive of RBD; and only one patient wished for RBD specific therapy with clonazepam 0.5 mg after revealing a diagnosis of RBD.

Sleep-Related Breathing Disorders

Twenty-four percent of patients were diagnosed with sleep-related breathing disorders: 14 had mild sleep apnea syndrome,

Table 2—Medication of the narcolepsy cohort

	Total group (n subjects)	Monotherapy (n subjects)
Wake enhancing medication	55	53
Modafinil	44	
Methylphenidate	13	
Sodium oxybate	4	2
Anticatataplectic medication	35	32
Clomipramine	22	
Fluoxetine	5	
Venlafaxine	5	
Reboxetine	5	
Protryptiline	1	

as defined by an apnea-hypopnea index (AHI) between 5-15/h; 8 moderate sleep apnea syndrome with an AHI between 15-30/h; and 2 had severe sleep apnea syndrome with an AHI > 30 /h. The majority had obstructive sleep apnea syndrome (21/24); 2/24 had mixed sleep apnea syndrome; and 1/24 central sleep apnea syndrome. The majority declined treatment when offered (18/24). Only the minority (6/24) accepted specific treatment for sleep-related breathing disorder when offered (5 nasal continuous positive airways pressure therapy, 1 intraoral device). All patients of the apnea treated group had moderate and severe sleep apnea syndrome. Men tended to have sleep apnea syndrome more often (19/56 vs. 5/44; $p = 0.063$) than women.

Restless Legs Syndrome

Twenty-four of the 100 narcolepsy patients had RLS. The majority of the affected patients (19/24) declined to receive specific treatment when offered. At the time of the clinical interview, only 3 patients (12.5%) were on a daily therapy with pramipexole 0.18-0.27 mg; 2 (8.3%) additionally took pramipexole 0.088-0.18 mg on demand.

Parasomnias and Additional Polysomnographic and MSLT Findings

Parasomnias were present in 34 patients. RBD affected 24 patients and NREM parasomnias affected 10 patients. Of note, only one of the 34 patients wished specific treatment when offered. REM sleep without atonia was present in most patients (90%). A periodic limb movement in sleep index > 5 /h was present in 75%. In addition, polysomnography revealed sleep fragmentation in 68% of cases, high frequency leg movements (hypnagogic foot tremor and alternating leg muscle activation during sleep) in 35% of cases, and excessive fragmentary myoclonus in 22% of cases. Frequency of cases with NREM parasomnias or periodic leg movements differed between NC and N patients (NC vs. N: 6/87 vs. 4/13, $p = 0.024$ and NC vs. N: 69/87 vs. 6/13, $p = 0.017$, respectively). Men more often had excessive fragmentary myoclonus (20/56 vs. 2/43; $p < 0.001$). There was a borderline association between a PLMS index > 5 /h and the presence of high frequency leg movements ($p = 0.055$).

MSLT recordings of 17 of the 24 narcolepsy patients with RBD were available for this review. A mean of 10.7 ± 3.2 min of REM sleep were analyzed for each MSLT run with REM

Table 3—Educational level of the Innsbruck narcolepsy cohort

	Total (n = 92)	NC (n = 82)	N (n = 10)	p-value
University degree	14 (15.2%)	14 (17.1%)	0 (0%)	N.A.
College	24 (26.1%)	18 (22.0%)	6 (60.0%)	0.014
Vocational education	44 (47.8%)	42 (51.2%)	2 (20.0%)	0.001
Compulsory schooling	10 (10.9%)	8 (9.8%)	2 (20.0%)	0.058

NC, narcolepsy with cataplexy; N, narcolepsy without cataplexy.

sleep. The percentage of 3-sec mini-epochs having “any” EMG activity in the chin was $55.8 \pm 18.2\%$. The SINBAR standard cutoff of 18% was exceeded in 13 of the 17 recordings. In 15 of the 17 recordings there was evidence of REM sleep without atonia when a cutoff of 15% was used.¹⁹ All video-recordings showed visible movement activity during REM sleep. According to the Sixel-Döring classification,²⁰ 11 recordings were rated as a 2, meaning that proximal limb movements including violent behaviors were present. Six recordings were rated as a 1, meaning that small movements or jerks were present. Vocalizations (meaning a score of 1) were present in 9 recordings.

Psychiatric Comorbidity

Psychiatric comorbidity based on patients’ charts was present in 8 cases (2 major depression, 2 bipolar disorder, 2 substance abuse disorder, 1 anxiety disorder, 1 first manic episode with psychotic symptoms [acoustic hallucinations of a religious content]). Psychiatric symptoms started prior to narcolepsy onset in 6 of these 8 patients, 2 patients developed psychiatric comorbidity after onset of narcolepsy (major depression, first manic episode with psychotic symptoms). At time of the clinical interview, psychiatric comorbidity was remitted in 3 of the 8 patients (2 substance abuse disorder, 1 manic episode with psychotic symptoms), and the remaining 5 had an ongoing psychiatric disease (2 major depression, 2 bipolar depression, 1 anxiety disorder).

Educational Level (N = 92), Employment-Related Aspects, and Information on Pregnancy

Educational level varied between patients ranging from subjects with a university degree (n = 14, 15.2%) to subjects with compulsory schooling of 9 years (n = 10, 10.9%). See **Table 3** for further information. NC patients had a higher educational level than N patients although this difference was only borderline significant (p = 0.08). Men and women had a comparable educational level (p = 0.226). At the time of last follow-up, 57/92 subjects had a regular job, 17/92 were retired (8 early, 9 regular retirement), 12/92 unemployed, 5/92 on maternity leave, and 1/92 were studying at university.

Forty-six of the 92 patients (50%) answered positively to the question if they had difficulties at their work place due to narcolepsy. Twenty-one of these 46 patients (45.6%) selected or switched their jobs in order to better cope with their disease.

Twenty-eight of the 44 female narcolepsy patients (63.6%) had at least one pregnancy. None of the patients reported disease-related complications during pregnancy. During delivery, 2 of the 44 patients reported on disease-related complications (sleep attacks during delivery, prolonged awakening after anes-

thesia). Seven patients reported disease-related complications in the time period after delivery (sleep attacks during breastfeeding: n = 6, problems due to excessive daytime sleepiness: n = 5, cataplexy when holding the baby: n = 1). Of note, only a minority of patients took wake-promoting or antiepileptic medication when becoming pregnant (1 modafinil, 1 methylphenidate, 2 clomipramine). Abnormalities of development or malformations were not observed.

DISCUSSION

The current study is one of the largest monocentric polysomnographic studies to date of patients with definite narcolepsy^{9,10} and confirms the frequent comorbidity of narcolepsy with many other sleep disorders, some of which were previously investigated in a small number of studies only.^{9,21-24} One of the key and original findings of our study is that minor motor abnormalities during sleep which are classified in the ICSD-2 as “isolated symptoms, apparently normal variants and unresolved issues” such as high frequency leg movements (alternative terms: hypnagogic foot tremor and alternating leg muscle activation during sleep) and excessive fragmentary myoclonus are common in narcolepsy patients with frequencies of 35% and 22%, respectively.

Other major findings are the considerable diagnostic delay between first symptoms and narcolepsy diagnosis, the diversity of narcolepsy symptoms and the various degrees of symptom severity as well as the marked proportion of significant sleep comorbidity in narcolepsy. In the present study, the median diagnostic delay is marked at with 6.5 years, with a range from 0 to 39 years. This diagnostic delay is well in line with that of other recent studies in both European and overseas countries.^{25,26} The presence of cataplexy surprisingly did not shorten the diagnostic interval. This might be explained by the fact that narcolepsy is still underrecognized by health care professionals. Especially in the light of the impact of a lifelong disabling diagnosis with important health, social and economic consequences such as narcolepsy,²⁷ careful education of healthcare professionals on narcolepsy is crucial to reduce the current diagnostic interval.

The clinical spectrum of narcolepsy in this cohort is broad, ranging from patients with the complete narcoleptic tetrad to patients whose only complaint is excessive daytime sleepiness. In the present study, 36/100 patients had all four cardinal symptoms of narcolepsy, 28/100 patients had three cardinal symptoms, 29/100 two cardinal symptoms, and 7 had only excessive daytime sleepiness. Symptom severity also varied. Cataplexy severity ranged from patients with daily severe cataplectic attacks which have led to serious self-injury in the past to patients

with only very few attacks with involvement of the head/neck only on rare occasions without any relevant subjective complaint. Sleep paralysis and hypnagogic hallucinations, which affected half of our subjects varied also markedly in their frequency and severity. Surprisingly, 62% of patients had a regular job, perhaps pointing to minor severity or excellent coping strategies. The percentage of unemployment or early retirement is lower to that reported in a German study, which found that 59% of the patient collective were unemployed mainly due to the disease itself.²⁸ Moreover, approximately one-third of subjects preferred to refrain from medication despite being offered or to take only on-demand medication when necessary, whereas two-thirds of patients needed a daily treatment of narcoleptic symptoms.

In addition, we confirmed and expanded the knowledge on sleep comorbidity in narcolepsy. Ninety percent of the patients had REM sleep without atonia and 24% had a diagnosis of RBD, indicating symptomatic RBD. In contrast to the idiopathic form of RBD,²⁹ RBD in narcolepsy affected both men and women equally. In addition, our findings confirm the results of Ferri et al. who demonstrated that in NC increased phasic and tonic electromyographic activity characteristic of REM sleep without atonia during REM sleep is present irrespective of the presence of a comorbidity of RBD.³⁰ Our findings of the presence of REM sleep without atonia in narcolepsy are consistent with those of other authors who found REM sleep without atonia in up to 50% of narcolepsy cases.²¹ However, their figure of 50% is still admittedly lower than our figure of 90%. Part of the reason for this discrepancy may be that these other authors used a quantitative 20% EMG cutoff of tonic EMG activity in the chin for the definition of RWA.²¹ We on the other hand evaluated the presence of RWA qualitatively in line with the currently valid ICSD-2 criteria.⁵ We assume when applying a 20% cutoff—which was arbitrarily chosen for RBD at that time—our frequency of RWA might also have been lower. Moreover, the frequency of RBD in our narcolepsy cohort is intermediate to the frequencies reported in the literature so far, ranging from 12% to 36%^{22,23} compared to 0.5% in the general population.^{31,32} Of note, EMG typical features of RBD were not only present during the nocturnal video-polysomnography but also during the MSLT recording, and up to 80% of our narcolepsy RBD patients were above the recently published RBD cutoff value of 18% during the MSLT.¹⁹

Of note, 75% of subjects had a periodic leg movement in sleep index > 5/h, and approximately 20% of patients fulfilled minimal diagnostic criteria for RLS.³³ In contrast, only a minority of patients considered themselves as needing treatment for the restless legs symptoms. The frequency of RLS is in line with a recent study showing that 15% of the investigated narcolepsy patients had RLS symptoms at least twice per week compared to 3% of age-matched controls.²⁴

The demonstration of a high amount of minor motor abnormalities during sleep in narcolepsy in the present study is consistent with a recent video analysis which demonstrated that motor events detected in time-synchronous video-polysomnography are very frequent during both NREM and REM sleep in narcolepsy patients compared to controls.³⁴ Of note, in narcoleptic children wakefulness-related motor disturbances are frequently observed at disease onset.³⁵ Based on high rates of REM sleep without atonia and periodic leg movements in sleep

in narcolepsy, one might suggest both sleep-related motor features and sleep fragmentation, (present in 68% of narcoleptics in this cohort) as additional hallmarks of narcolepsy, while insomnia, which was present in 28% of patients, does not exclude a diagnosis of narcolepsy.

Twenty-four percent of the patient cohort had predominantly obstructive sleep apnea syndrome. This frequency is increased compared to a prevalence of 4% in the general population,³⁶ and is similar to the findings of other large studies in narcolepsy with prevalences ranging from 18% to 29%.^{10,37,38} The finding of multiple sleep comorbidities in narcolepsy strongly corroborates the recommendation of the ICSD-2 criteria to perform polysomnography even in definite NC. Of 100 narcolepsy patients in this series, all but 4 could be diagnosed based on clinical history and multiple sleep latency testing alone, suggesting that cerebrospinal fluid examinations for hypocretin/orexin levels are not a diagnostic necessity.

Obesity defined as a BMI > 30 kg/m² was present in 23% of narcolepsy patients. Moreover, patients with narcolepsy in this cohort had a 1.5-fold increased percentage of subjects with BMI percentiles above 90, which was somewhat lower than the rate of obesity in narcolepsy reported by a German study (which found a mean BMI percentile of 75 and a three-fold increased percentage of subjects with BMI percentiles above 90),³⁹ and a Norwegian study which found that 29% of narcolepsy patients were obese.⁴⁰ An association between obesity and the presence of cataplexy and hence a decreased or undetectable hypocretin/orexin level has been claimed by some authors.^{41,42} In the present cohort, there was no difference between NC and N patients in regard to BMI, although this comparison is of limited value given the small sample size of 13 patients in the N group.

Findings of the current study revealed that presence of cataplexy went along with more severe excessive daytime sleepiness, more severe and frequent sleep paralysis, and sleep-related hallucinations, as well as more sleep onset REM episodes and a higher association with DQB1*0602 and DQB1*0501, suggesting a continuum between N with milder disease features and NC with more severe features. Earlier clinical observation that men are more severely affected by narcolepsy than women was not confirmed by our study. On the contrary, women scored higher than men on the Epworth Sleepiness Scale.

One of the strengths of the present study is that all included patients had symptoms of narcolepsy as their initial clinical presentation. Thus we feel that our findings are more likely to be generalizable to the general population of narcolepsy patients, barring the possibility that a community sample of narcoleptics could be milder and thus less likely to have as many comorbid sleep disorders. A polysomnographic study of a community sample is needed to further verify our findings. In addition, multicenter studies are highly warranted, as increasing substantially the number of patients allows for multivariate approaches.

Another potential caveat of this study is that questions on symptom onset were assessed retrospectively. Therefore some wrong estimations cannot totally be excluded.

In summary, this study demonstrates that the clinical spectrum of narcolepsy is broad in regard to symptom diversity and severity. Whether this clinical spectrum is responsible for the marked diagnostic delay of this disease remains speculative. Moreover, sleep comorbidities in narcolepsy are a non-trivial

issue, which is an additional argument in favor of the use of polysomnography for a definite diagnosis of narcolepsy. Based on our data, presence of REM sleep without atonia, periodic leg movement in sleep indices $> 5/h$, and sleep fragmentation can be regarded as further polysomnographic hallmarks of the disease, whereas insomnia does not speak against a diagnosis of narcolepsy. The new finding of a high percentage of narcolepsy patients with high frequency leg movements as well as excessive fragmentary myoclonus adds to the literature suggesting that narcolepsy, in general, is characterized by motor instability.

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