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SCIENTIFIC INVESTIGATIONS

Narcolepsy type 1 features across the life span: age impact on clinical and polysomnographic phenotype

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Study Objectives: Narcolepsy type 1 (NT1) is a chronic neurological disorder typically arising during adolescence and young adulthood. Recent studies demonstrated that NT1 presents with age-specific features, especially in children. With this study we aimed to describe and to compare the clinical pictures of NT1 in different age groups.

Methods: In this cross-sectional, multicenter study, 106 untreated patients with NT1 enrolled at the time of diagnosis underwent clinical evaluation, a semistructured interview (including the Epworth Sleepiness Scale), nocturnal video-polysomnography, and the Multiple Sleep Latency Test. Patients were enrolled in order to establish 5 age-balanced groups (childhood, adolescence, adulthood, middle age, and senior).

Results: The Epworth Sleepiness Scale score showed a significant increase with age, while self-reported diurnal total sleep time was lower in older and young adults, with the latter also complaining of automatic behaviors in more than 90% of patients. Children reported the cataplexy attacks to be more frequent (> 1/d in 95% of patients). "Recalling an emotional event," "meeting someone unexpectedly," "stress," and "anger" were more frequently reported in adult and older adult patients as possible triggers of cataplexy. Neurophysiological data showed a higher number of sleep-onset rapid eye movement periods on the Multiple Sleep Latency Test in adolescent compared to senior patients and an age-progressive decline in sleep efficiency.

Conclusions: Daytime sleepiness, cataplexy features and triggers, and nocturnal sleep structure showed age-related difference in patients with NT1; this variability may contribute to diagnostic delay and misdiagnosis.

Keywords: narcolepsy type 1, sleepiness, cataplexy, emotional triggers, nocturnal sleep

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with narcolepsy type 1 experience excessive daytime sleepiness, cataplexy, and disrupted nocturnal sleep, which typically appear at a young age. However, patients with disease onset during childhood or older adulthood may represent a diagnostic challenge, and slight differences in narcolepsy type 1 phenotype have been reported at distinct life stages, sometimes with discordant findings.

Study Impact: Comparing for the first time both clinical and polysomnographic features of narcolepsy type 1 in a large number of untreated patients of different age groups, our study documented substantial modifications in the disease presentation with age, even though further investigations are required to confirm and extend our findings. Awareness of these age-dependent phenotypes will facilitate narcolepsy type 1 recognition among different specialists and could advantageously shorten the long diagnostic delay.

INTRODUCTION

Narcolepsy type 1 (NT1) is a rare, lifelong, central disorder of hypersomnolence,[1] with an estimated prevalence of 0.047% in the European population.[2] NT1 is pathophysiologically linked to the selective loss of hypocretin-1-producing neurons in the hypothalamus, most likely due to an autoimmune process.[3,4]

NT1 onset typically occurs during adolescence and young adulthood, with a bimodal distribution (first peak at around age 15 years, second peak at age 35 years),[5,6] and the first symptom appears during childhood (defined up to age 10 or 12 years in different studies) in at least 8%–15% of patients,[5,7,8] while a late occurrence is extremely rare (0.71% of patients after age 60 years).[9] Patients with disease onset at a very early or late age,

as well as positive first-degree familial history for symptoms of narcolepsy, should be regarded as red flags for symptomatic or genetic forms.[10–12]

Although the disease arises at a young age in most patients, NT1 diagnosis is usually established with a long delay,[7] negatively affecting the treatment opportunities and, consequently, the disease burden.[13,14] Although the increasing awareness of narcolepsy has shortened the diagnostic gap in many countries,[7,9] it still remains substantial in central Europe (around 8.9 years).[14]

Since its first description, the narcolepsy with cataplexy (now NT1) picture has been well characterized in adult patients and comprises excessive daytime sleepiness (EDS), untimely manifestations of dissociated rapid eye movement (REM) sleep (ie, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucination, REM sleep behavior disorder),[15,16] and disrupted nocturnal sleep (DNS).[16] Nonetheless, slight differences in NT1 clinical and polysomnographic phenotypes have been reported at distinct life stages, and a peculiar, partially remitting cataplexy presentation has been described in pediatric patients,[9,17–19] consisting of a complex movement disorder with both "negative" (ie, hypotonic) and "active" (ie, hyperkinetic) motor features.[18–20] In these patients, near to disease onset, hypotonia may occur subcontinuously, presenting with a characteristic "cataplectic facies" and ataxic gait, even in the absence of emotional triggers.[18,19,21]

Moreover, children with NT1 frequently present with hyperactivity, attention difficulties, irritability, and depressive symptoms,[22–26] and pediatric NT1 has been associated with a high prevalence of obesity and precocious puberty.[26–28] NT1 arising in older adult patients, instead, may present with unusual features that mimic a movement disorder or even an acute cerebrovascular disease.[11,12]

While a discrete pediatric NT1 clinical picture has been extensively reported and recognized, reports on the effect of the other life stages on the NT1 clinical and polysomnographic aspects remain sparse and sometimes discordant.[5,8,26,29]

Therefore, the aim of the present study was to investigate possible differences in NT1 presentation across the life span and to characterize untreated patients of distinct age groups.

METHODS

Participants

This cross-sectional, multicenter study included 106 patients with NT1 recruited from several sleep centers in Italy, in order to establish 5 balanced age groups (roughly 20 patients for each group) at diagnosis: (1) children = younger than 11 years old (n = 20), (2) adolescents = 11–18 years old (n = 21), (3) adults = 19–44 years old (n = 23), (4) middle-aged = 45–64 years old (n = 22), and (5) seniors = 65 years old or older (n = 20). Patients were consecutively recruited from June 2015 to June 2016 within each age group. The diagnosis of NT1 fulfilled the current *International Classification of Sleep Disorders* (third edition) criteria.

All patients had cataplexy and were drug-naïve at the time of neurophysiological evaluations and clinical interview. Patients with other neurological disorders and/or cognitive impairments were excluded from our study. The time gap between cataplexy onset and NT1 diagnosis was shorter than 15 years in 81/106 (76.4%) patients.

The study was approved by the Local Health Trust's Ethics Committee of the center of reference (Comitato Etico Interaziendale Bologna-Imola, Protocol number 17009), and all participants provided written informed consent at the time of inclusion.

Assessment

All patients underwent a standardized diagnostic protocol encompassing clinical evaluation performed by a sleep expert neurologist or pediatric neurologist, anthropometric assessment comprehensive of body mass index (BMI), and self-reported EDS assessment using the Epworth Sleepiness Scale (ESS). In pediatric patients (aged < 18 years), a modified ESS version was used,[26,30,31] and BMI percentile was determined according to the Italian growth percentile scales for boys and girls[32]: Obesity was defined as BMI > 95th percentile, overweight as BMI between the 85th and 95th percentile, and normal weight as BMI < 85th percentile.

The diagnostic protocol encompassed nocturnal polysomnography (PSG) followed by the 5-nap Multiple Sleep Latency Test (MSLT), and, whenever possible, lumbar puncture for cerebrospinal fluid hypocretin-1 assay.

PSG and the MSLT were scored by a board-certified polysomnographic technician blinded to the clinical status of patients. Sleep data (sleep latency; REM sleep latency; time in bed; total sleep time; wakefulness after sleep onset; sleep efficiency; percentages of total sleep time spent in different sleep stages, namely non-REM sleep stages 1, 2, 3 [N1, N2, N3], and REM sleep; apnea-hypopnea index; and periodic limb movement index) and MSLT results (mean sleep latency and number of sleep-onset REM sleep periods) were collected. A positive MSLT was registered in 105/106 (99.1%) patients, and in the remaining patient NT1 diagnosis was based on cataplexy presence and cerebrospinal fluid hypocretin-1 deficiency. Lumbar puncture was performed in 82/106 (77.4%) patients and low or absent cerebrospinal fluid hypocretin-1 levels were found in all of them.

In order to investigate specific features of EDS-, cataplexy-, and narcolepsy-associated symptoms, patients underwent a semistructured interview. Pediatric patients were interviewed in the presence of parents, who were allowed to contribute to their child's answers when needed.

In the absence of validated tools, the interview was designed with reference to recent studies, to the most influential validated questionnaire in the field,[33–36] and to the clinical practice experience of the sleep disorders specialists participating in this study.

The interview lasted approximately 60–90 minutes and was divided into 3 sections. The first one explored EDS features, including age at onset (years) and the presence or absence of (1) sleep prodromal signs; (2) scheduled naps, together with their duration (minutes); and (3) automatic behaviors, irritability, and REM sleep behavior disorder (RBD) episodes during daytime naps. Diurnal total sleep time (h/d) was also investigated. The second part focused on the clinical characteristics of cataplexy:

Table 1—General characteristics and nocturnal polysomnography data.

	Children Aged < 11 Years (n = 20)	Adolescents Aged 11–18 Years (n = 21)	Adults Aged 19–44 Years (n = 23)	Middle-Aged Patients Aged 45–64 Years (n = 22)	Seniors Aged > 64 Years (n = 20)	*P* (1-way ANOVA)
Demographic and clinical data						
Male/female, n	14/6	8/13	15/8	12/10	7/13	ns
Overweight/obese (%)	55	67	73	100	90	< .005[a]
Hypersomnolence age at onset, y	6.8 ± 1.64	11.9 ± 3.02	19.6 ± 7.20	34.7 ± 14.34	38.1 ± 21.27	< .0001
Cataplexy age at onset, y	6.8 ± 1.51	11.6 ± 2.56	21.0 ± 8.63	40.2 ± 14.59	43.7 ± 19.25	< .0001
Sleep paralysis (%)	15	52	70	59	40	< .01[a]
Sleep paralysis age at onset, y	6.7 ± 2.08	11.4 ± 2.91	22.2 ± 8.82	37.1 ± 15.23	45.7 ± 18.92	< .0001
Hypnagogic/hypnopompic hallucinations (%)	45	67	61	82	60	ns[a]
Hypnagogic/hypnopompic age at onset, y	6.6 ± 1.51	12.4 ± 2.95	20.8 ± 7.07	40.1 ± 12.42	45.2 ± 14.92	< .0001
Disrupted nocturnal sleep (%)	100	100	87	95	70	< .005[a]
Disrupted nocturnal sleep age at onset, y	6.4 ± 1.37	10.7 ± 3.69	21.4 ± 7.76	36.5 ± 14.61	40.5 ± 19.76	< .0001
Delay from hypersomnolence onset to diagnosis, y	1.3 ± 1.53	2.3 ± 2.22	12.3 ± 9.42	18.9 ± 13.56	32.6 ± 20.55	< .0001
Delay from cataplexy onset to diagnosis, y	1.3 ± 1.56	2.6 ± 2.06	10.0 ± 9.57	13.4 ± 12.43	27.0 ± 18.06	< .0001
Sleep architecture						
Time in bed, min	565.7 ± 66.24	499.7 ± 44.08	475.1 ± 90.43	473.7 ± 84.77	490.9 ± 86.25	< .005
Total sleep time, min	512.8 ± 59.51	446.0 ± 53.87	371.0 ± 88.49	390.5 ± 83.16	361.8 ± 88.91	< .0001
Sleep latency, min	3.9 ± 3.78	3.1 ± 2.41	4.9 ± 3.17	7.2 ± 9.42	7.4 ± 6.64	ns
REM sleep latency, min	21.8 ± 37.04	29.5 ± 60.55	48.7 ± 60.92	55.6 ± 62.44	64.5 ± 81.65	ns
Wakefulness after sleep onset, min	49.0 ± 37.45	50.5 ± 39.27	90.1 ± 52.15	94.2 ± 50.38	131.5 ± 72.64	< .0001
Sleep efficiency (%)	91.1 ± 6.20	89.1 ± 7.32	79.2 ± 10.96	78.7 ± 9.23	72.3 ± 13.94	< .0001
Sleep stage N1 (%)	12.3 ± 5.30	10.3 ± 5.00	15.5 ± 6.30	16.7 ± 7.62	23.1 ± 17.92	< .005
Sleep stage N2 (%)	35.1 ± 4.44	44.1 ± 8.38	42.5 ± 8.92	45.1 ± 10.15	33.1 ± 7.42	< .001
Sleep stage N3 (%)	26.2 ± 6.51	21.7 ± 7.32	19.0 ± 5.35	12.5 ± 5.45	23.9 ± 7.62	< .0001
REM sleep stage (%)	26.5 ± 5.43	23.8 ± 6.62	23.0 ± 5.13	26.2 ± 7.49	22.7 ± 14.74	ns
AHI (events/h)	0.27 ± 0.74	0.9 ± 2.77	6.8 ± 9.13	12.2 ± 14.23	17.2 ± 16.75	< .0001
PLMI (events/h)	14.6 ± 14.50	7.9 ± 12.98	15.4 ± 13.85	33.6 ± 36.15	26.2 ± 18.14	.002

Values are presented as mean ± SD unless otherwise indicated. [a]Chi-square. AHI = apnea-hypopnea index, ANOVA = analysis of variance, ns = not significant, PLMI = periodic limb movement index, REM = rapid eye movement, SD = standard deviation.

Table 2—Sleepiness and MSLT data.

Daytime sleepiness data	Children Aged < 11 Years (n = 20)	Adolescents Aged 11–18 Years (n = 21)	Adults Aged 19–44 Years (n = 23)	Middle-Aged Patients Aged 45–64 Years (n = 22)	Seniors Aged > 64 Years (n = 20)	*P*
ESS[a]	13.19 ± 4.21	15.30 ± 4.09	15.78 ± 4.85	18.06 ± 2.33	19.07 ± 2.84	< .0005
Prodromal signs to sleep (%)	60	71	78	91	65	ns
Scheduled naps, presence (%)	45	67	48	32	45	ns
Nap duration, min	71.9 ± 20.98	82.50 ± 45.52	36.69 ± 24.83	87.5 ± 79.96	46.9 ± 44.19	ns
Diurnal total sleep time, h	2.6 ± 1.12	2.50 ± 1.20	1.6 ± 1.16	2.5 ± 2.03	1.7 ± 1.17	ns
REM sleep behavior disorder during nap, (%)	0	5	5	35	26	< .005
Automatic behaviors (%)	55	71	91	82	55	< .05
Irritability, (%)	90	90	74	64	25	< .0001
Neurophysiological data						
MSLT–sleep latency, min	4.4 ± 3.86	3.5 ± 3.08	2.9 ± 1.73	4.4 ± 3.91	3.9 ± 2.80	ns
MSLT–SOREMPs, number	3.9 ± 1.10	4.5 ± 0.87	4.3 ± 0.97	3.7 ± 1.35	3.5 ± 1.02	< .05[b]

Values are presented as mean ± SD unless otherwise indicated. One-way analysis of variance was used for group comparisons unless otherwise indicated. aIn patients < 18 years, a modified ESS version was used. bKruskal-Wallis analysis of variance. ESS = Epworth Sleepiness Scale, MSLT = Multiple Sleep Latency Test, ns = not significant, REM = rapid eye movement, SD = standard deviation, SOREMPs = sleep-onset REM sleep periods.

age at onset (years), frequency of cataplectic attacks (< 1/mo, ≥ 1/mo, or ≥ 1/d), duration of episodes (< 10 seconds, 10–120 seconds, or > 120 seconds), presence or absence of a "time-of-day effect" on cataplexy occurrence (a time of day in which cataplexy is more likely to occur), and the use of strategies to control or avoid cataplexy attacks. Particular attention was paid to cataplexy triggers and a wide range of events were investigated (namely, "laughter," "telling/listening to jokes," "euphoria," "recalling an emotional event," "meeting someone unexpectedly," "surprise," "anger," "stress," "embarrassment," "fear," and "sexual intercourse"). In the third section, sleep paralysis, hypnagogic/hypnopompic hallucinations and DNS were investigated by assessing their occurrence, age at onset (years), and frequency (< 1/mo, ≥ 1/mo, or ≥ 1/d), as well as the number of awakenings per night for DNS.

Statistical analysis

For analytical purposes, patients were a priori divided into 5 different groups, based on age at NT1 diagnosis: children, adolescents, adults, middle-aged, and seniors. Data for each group are presented with descriptive statistics (mean ± standard deviation for continuous variables and percentages for categorical data). Group differences were analyzed with the chi-square test, the 1-way analysis of variance, and the Kruskal-Wallis analysis of variance followed by posthoc comparisons. Analyses were conducted using SPSS 19.0 (SPSS, Inc., Chicago, IL); results with alpha level < .05 were considered statistically significant.

RESULTS

General characteristics and nocturnal polysomnography

Clinical data and nocturnal sleep architecture parameters are reported in **Table 1**.

Significant group differences were observed in BMI, with middle-aged patients being more likely to present with overweight/obesity than children ($P < .0001$), adolescents ($P < .005$), and adults ($P < .005$). Children with NT1 were less likely to report sleep paralysis at disease onset than adolescents ($P < .05$), adults ($P < .0001$), and middle-aged patients ($P < .005$). The percentage of patients presenting with DNS at diagnosis was significantly different, with seniors reporting this symptom more frequently than children ($P < .01$), adolescents ($P < .01$), and adults ($P < .05$). Regarding nocturnal video-PSG data, children with NT1 spent more time in bed than adults and middle-aged patients ($P < .005$) and had higher total sleep time than adults, middle-aged patients, and seniors ($P < .0001$); adolescents with NT1 also had significantly higher total sleep time than adults and seniors ($P < .05$). Sleep continuity differed between groups, with children and adolescents with NT1 presenting with higher sleep efficiency than adults, middle-aged patients ($P < .005$ and $P < .05$, respectively), and seniors ($P < .0001$), while seniors had more wakefulness after sleep onset than children and adolescents ($P < .0005$). Sleep stages representation also differed between groups: N1 percentage was higher in seniors with NT1 than in children ($P < .05$) and adolescents ($P < .01$), N2 was less represented in children than in adolescents and middle-aged patients ($P < .01$), and N3 percentage was lower in middle-aged patients with NT1 than in children ($P < .0001$), adolescents ($P < .005$), and seniors ($P < .05$). Apnea-hypopnea index differed between groups, with middle-aged and senior patients showing higher values than children and adolescents ($P < .005$), and periodic limb movement index was significantly lower in adolescents compared to middle-aged patients ($P = .008$).

EDS features and MSLT

Data on EDS and the MSLT are reported in **Table 2.** Children with NT1 showed lower ESS scores than middle-aged patients ($P < .005$) and seniors ($P < .0001$). No differences were found in

Table 3—Cataplexy features.

Features	Children Aged < 11 Years (n = 20)	Adolescents Aged 11–18 Years (n = 21)	Adults Aged 19–44 Years (n = 23)	Middle-Aged Patients Aged 45–64 Years (n = 22)	Seniors Aged > 64 Years (n = 20)	*P* (χ^2)
Cataplexy frequency (%)						
≥ 1/d	95	57	52	50	40	
≥ 1/mo	5	43	44	41	45	< .05
< 1/mo	0	0	4	9	15	
Cataplexy duration (%)						
< 10 s	45	43	48	36	35	
10–120 s	55	57	35	36	40	ns
> 120 s	0	0	17	27	25	
Time-of-day effect on cataplexy (%)	65	38	22	32	25	< .05
Use of strategies to avoid cataplexy attack (%)	25	38	30	36	15	ns
Use of strategies to control cataplexy attack (%)	65	90	78	64	65	ns
Cataplexy triggers						
Laugh (%)	100	100	96	95	85	ns
Telling/listening to jokes (%)	75	86	61	82	80	ns
Euphoria (%)	45	48	65	68	55	ns
Recalling an emotional event (%)	5	19	22	36	45	< .05
Meeting someone unexpectedly (%)	5	20	53	82	70	< .0001
Surprise (%)	45	38	65	50	70	ns
Anger (%)	20	38	74	73	55	< .005
Stress (%)	10	14	17	45	30	< .05
Embarrassment (%)	20	20	48	23	50	ns
Fear (%)	35	38	32	36	40	ns
Sexual intercourse (%)	—	—	17	18	0	ns

ns = not significant.

presence or duration of self-reported diurnal naps, while RBD episodes during naps were more commonly reported in middle-aged patients than in children ($P < .01$), adolescents ($P < .05$), and adults ($P < .05$); seniors with NT1 also reported increased occurrence of RBD during naps compared to children ($P < .05$). Automatic behaviors were more frequently reported by adults compared to children, adolescents, and seniors (all $P < .01$). Conversely, senior patients were less likely to report irritability compared to middle-aged ($P < .05$), adult ($P < .001$), and younger patients with NT1 (children and adolescents, all $P < .0001$). On the MSLT, no difference was observed in mean sleep latency, but adolescents presented a higher number of sleep-onset REM sleep periods than seniors ($P < .05$).

Cataplexy

Data on cataplexy features and triggers are reported in **Table 3.** Children with NT1 were more likely to manifest 1 or more cataplexy episodes per day than adolescents ($P < .005$), adults ($P < .01$), middle-aged patients ($P < .005$), and seniors ($P < .001$), without differences in attack duration. Furthermore, children with NT1 were more likely to report a time-of-day effect on cataplexy occurrence than adults ($P < .005$), middle-aged patients ($P < .05$), and seniors ($P < .05$).

Regarding cataplexy triggers, seniors and middle-aged patients were more likely to report that cataplexy could be associated with the "recall of an emotional event" than children with NT1 ($P < .005$ and $P < .05$, respectively). Moreover, middle-aged patients were more likely to experience cataplexy when "meeting someone unexpectedly" compared to children ($P < .0001$), adolescents ($P < .005$), and adults ($P < .05$); "meeting someone unexpectedly" also more frequently triggered cataplexy in seniors than in children ($P < .0001$) and adolescents ($P < .001$). Finally, middle-aged patients were more likely to report "stress" as a cataplexy trigger than children, adolescents, and adults (all $P < .05$), while "anger" was a more common trigger in adults than in children ($P < .0001$) and adolescents ($P < .05$); similarly, middle-aged patients were more likely to report cataplexy associated with "anger" than were children ($P < .001$) and adolescents ($P < .05$).

DISCUSSION

In this study we directly compared both clinical and polysomnographic characteristics of drug-naïve patients with NT1 of different age groups, covering the whole lifespan. We found

substantial differences in the clinical features of EDS, cataplexy, and nocturnal sleep structure.

Concerning MSLT data, the increased occurrence of sleep-onset REM sleep periods in adolescents mirrors previous findings.[8,29,37] Conversely, the absence of differences in MSLT sleep latency may have been influenced by the relatively small size of the sample.[29] By contrast, self-reported sleepiness (as measured by the ESS) showed a significant increase with age, a difference from other questionnaire-based studies contrasting 2 or 3 age groups that found no modifications.[5,26,33] Despite their higher ESS scores, our older adult patients reported shorter naps and shorter self-estimated diurnal total sleep time (although not statistically significant), possibly pointing to sleep misperception. A similar underperception of diurnal naps has already been described in patients with central hypersomnias and obstructive sleep apnea syndrome, without age-related differences, and may have contributed to diagnostic delay.[38]

With regard to our adult patients with NT1, the reduced self-estimated diurnal total sleep time, together with the highest prevalence of automatic behaviors (even higher than what has been reported in the literature),[16] could represent the attempt of these patients to cope with social, work, and/or family commitments despite EDS.

Furthermore, our findings confirmed that irritability is a typical symptom of narcolepsy in children, as widely reported in the previous literature.[22,23] Finally, since RBD episodes during diurnal naps have been documented in younger patients with NT1,[31,39] we investigated their occurrence in our sample through clinical interview, finding a predictable higher prevalence in middle-aged and senior patients (around 30%).[40] Patients younger than age 19 years, instead, reported a lower prevalence of RBD (approximately 2.5%), likely due to the less complex and violent phenotype of RBD episodes in patients with NT1[41] that might escape the attention of family members. This could explain the discrepancy with a previous PSG study that showed a very high occurrence of RBD (around 17.5%) up to a condition of "status dissociatus" also in children with NT1.[31]

Several studies consistently showed that both adult and young patients with narcolepsy also experience DNS, differently characterized by frequent and prolonged awakenings as well as by increased nocturnal transitions between sleep stages.[16,42] A decline in sleep efficiency and an increase in prevalence of conditions such as sleep-disordered breathing or periodic limb movements occur during normal aging[43] and are common in narcolepsy[5,37,44]; however, in patients with NT1, sleep-disordered breathing and periodic limb movements are rarely severe,[44] and these nocturnal features are not mirrored by an age-related increase in EDS.[5,44] Our nocturnal PSG results showed a progressive worsening of DNS with age, associated with higher sleep-disordered breathing and periodic limb movements indices as already reported,[9,44] and paralleled by increased ESS scores, while objective sleep propensity on the MSLT and self-reported diurnal total sleep time paradoxically suggested milder sleepiness in older adults.

We extensively addressed cataplexy clinical features: A significantly higher cataplexy frequency was found in children with NT1 compared to the other age groups, since almost all of them (95%) reported daily cataplectic attacks (while the percentage dropped to a 40%–60% range in all other patients). A progressive decrease with age in cataplexy frequency has already been documented in the literature,[29,33] but seldom.[8] Higher representation of both "negative" and "positive" motor phenomena is typical of childhood NT1 around onset.[18,19]

As suggested by other questionnaire-based reports, "tiredness" could be associated with more frequent cataplexy[35,45]; in our sample, a time-of-day effect in cataplexy occurrence was commonly signaled only by children.

While many studies have already focused on the identification of cataplexy triggers,[35] on their emotional tone ("positive," "negative," or "undefined"),[34,36] and even on their possible absence (spontaneous attacks) in the pediatric population,[18] to date no study has assessed whether those triggers vary across the lifespan. We found that some emotional stimuli ("recalling an emotional event," "meeting someone unexpectedly," "stress," and "anger") showed statistically significant differences through lifetime, being uncommon triggers in children and adolescents, but frequent in middle-aged patients and seniors. As mentioned above, hypotonic features appear in children with NT1 even in the absence of emotional stimuli and can become subcontinuous or permanent,[18] making it difficult to recognize clear cataplexy triggers. This may in part explain the low percentage of patients younger than age 19 years who reported emotional triggers differing from "laughter." Moreover, our findings could partially find an explanation in the intrinsic age-related nature of the investigated stimuli: Older patients have more time to collect emotionally relevant memories, while stress is an impactful factor in the daily routine of middle-aged patients, still struggling with work, social, and family commitments. Similarly, an unexpected encounter might be uncommon in infancy and adolescence but comes with a major emotional load in adults and especially in older adults.

Interestingly, while previous studies associated negative emotions with psychogenic cataplexy-like attacks (or "pseudocataplexy"),[46–48] in our sample "anger" and "stress" were reported as evocative of cataplexy in a high percentage of adult, middle-aged, and older adult patients with NT1, further challenging the concept of "typical" cataplexy when addressed only by history-taking.

Eventually, NT1 onset is frequently accompanied by overweight and obesity, and in adults a BMI > 25 kg/m^2 is observed in approximately 75% of patients,[49] which is consistent with our results (73%). Excessive BMI represents a significant medical comorbidity also in prepubertal patients with NT1.[20,27,28] According to a recent paper,[26] obesity occurs more frequently in patients younger than age 18 years (54% vs 17%), while overweight is more prevalent in adults (13% vs 44%). In our sample, the cumulative prevalence of overweight and obesity was significantly lower in children and adolescents compared to middle-aged patients; as the BMI categorization used in the pediatric population varies between different studies (eg, percentiles, standard deviation, *z*-score), comparisons are challenging and the prevalence of excessive body weight in children with NT1 ranges between 25% and 74%.[17,27,28]

Our study also comes with limitations. First, although 106 patients were enrolled, the number of patients within each age

group was relatively limited, influencing the results in terms of significance and of individual contribution to the outcomes (ie, higher impact of the outliers). Moreover, the establishment of a priori cutoff ages for the 5 groups, despite the intent to reflect recognizable life stages, may have influenced our results. Second, we recruited exclusively patients of Caucasian origin, thus precluding the possibility to compare disease features across different ethnic groups. Third, the semistructured interview we used was not validated by previous studies. Finally, we chose to focus on the clinical picture of NT1 in groups of different ages at diagnosis and not to take into account the disease duration; we are aware that including patients with different delay in diagnosis may represent a confounding factor in the clinical presentation, given the peculiar features at disease onset already documented in children[19] and the ability to cope with the symptoms that patients with a longer diagnostic delay may have developed.

In summary, some of our findings, including the number of sleep-onset REM sleep periods at MSLT and cataplexy frequency could suggest a higher impact of NT1 core symptoms in younger patients (children and adolescents), as previously reported by Dauvilliers and coauthors,[29] while a recent study contrasting patients with NT1 diagnosed before and after age 18 years failed to find any differences in ESS score and in cataplexy frequency.[26] On the other hand, our result on ESS score and sleep structure indicated a worsening of EDS and DNS with age.

Further investigations are thus required to confirm and extend our findings, in order to obtain a more comprehensive understanding of the underlying mechanisms.

Our study documented that NT1 presentation in drug-naïve conditions varies with age, an underestimated aspect that should be considered in the overall effort to promote disease awareness among different specialists[50] and shorten the diagnostic delay.

ABBREVIATIONS

BMI, body mass index
DNS, disrupted nocturnal sleep
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
MSLT, Multiple Sleep Latency Test
NT1, narcolepsy type 1
PSG, polysomnography
RBD, REM sleep behavior disorder
REM, rapid eye movement

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DISCLOSURE STATEMENT

All authors have reviewed and approved the manuscript. Work was performed at IRCCS, Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy. Oliviero Bruni has served as a consultant and provided expert testimony for both Angelini and Farmaceutici S.p.A. outside the submitted work. Luigi Ferini-Strambi participated in an advisory board for UCB Pharma and Jazz Pharmaceuticals outside the submitted work. Andrea Romigi participated in an advisory board for Eisai and for UCB Pharma outside the submitted work. Giuseppe Plazzi participated in an advisory board for UCB Pharma, Jazz Pharmaceuticals, Bioprojet, and Idorsia outside the submitted work. The other authors report no conflicts of interest.