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A comparison of mood, quality of life and executive function among narcolepsy type 1 patients with or without ADHD symptoms in China

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ABSTRACT

Objective: To investigate the prevalence of core attention-deficit/hyperactivity disorder (ADHD) symptoms in Chinese narcolepsy type 1 (NT1) patients and to explore mood, quality of life, and executive function in narcolepsy patients with or without ADHD and the response to Methylphenidate Hydrochloride Extended-release tablets (ER-MPH) treatment.

Method: A total of 267 pediatric NT1 patients (194 males and 73 females, 5–17 years old) were evaluated for ADHD symptoms by a psychiatrist using the DSM-IV diagnostic criteria of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid) from February 2011 to July 2013 at Peking University People's Hospital. All patients underwent Stanford Sleep Inventory (SSI) evaluation and polysomnography followed by multiple sleep latency tests (MSLT) before ER-MPH treatment. Neuropsychological evaluations, including the Inventory of Subjective Life Quality (ISLQ), Depression Self-resting Scale for Children (DSRS-C), Screening for Child Anxiety-related Emotional Disorders (SCARED) and Barratt Impulsiveness Scale (BIS), were performed before and after 16 weeks of ER-MPH treatment. Executive abilities were assessed by the Behavior Rating Inventory of Executive Function-parent version (BRIEF-P). The narcolepsy symptoms, evaluated by the Pediatric Sleep Questionnaire (PSQ), and ADHD symptoms were assessed before and after treatment in NT1 patients with ADHD.

Result: Seventy-seven of 267 (28.8%) NT1 patients had ADHD symptoms, with 73 patients being inattentive type (ADHD-I) and 4 patients being combined type (ADHD-C). Despite similar objective sleep parameters, NT1 patients with ADHD symptoms experienced higher anxiety levels, more impulsive behaviors, lower health-related quality of life and worse executive functions than those without ADHD ($p<0.05$). Methylphenidate treatment was effective in improving daytime sleepiness in NT1 patients with ADHD (PSQ, 16.7 ± 2.1 vs 13.5 ± 1.9, $p<0.05$) but was ineffective on ADHD symptoms (ADHD-RS, 25.3 ± 9.1 vs 26.4 ± 8.9, $p>0.05$).

Conclusion: A high prevalence of ADHD (28.8%) was identified in children and adolescents with NT1. Comorbid ADHD symptoms were associated with increased levels of mood disorders and lower quality of life. ER-MPH treatment could reduce daytime sleepiness but not ADHD symptoms in narcolepsy patients with ADHD, suggesting that new treatment strategies are needed for this group of patients.

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1. Introduction

Narcolepsy is characterized by excessive daytime sleepiness (EDS), cataplexy (sudden loss of muscle tone while awake, typically triggered by strong emotion), sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep (DNS) with fragmented sleep and awakenings [1]. Narcolepsy type 1 (NT1) is accompanied by a selective loss of orexin/hypocretin neurons in the lateral hypothalamus caused by yet unclear mechanisms. NT1 is associated with high rates of comorbidities [2], low educational level,

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employment rate and income [3], decreased quality of life [4,5], and increased mortality [6].

The symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) are frequently reported in narcolepsy patients. One retrospective study and two cross-sectional studies found that 20%–35.5% of narcolepsy patients had ADHD, which is four to eightfold higher than in the general population, indicating a close relationship between narcolepsy and ADHD [7–9]. A recent systematic review including five studies to assess the prevalence of ADHD symptoms in narcolepsy showed that the prevalence of ADHD symptoms was >30% [10]. However, the systematic review only included five studies, and the diagnostic criteria for ADHD and narcolepsy differed among five studies, thus, more research is needed to support the prevalence of ADHD symptoms in narcolepsy.

ADHD is a common neuropsychiatric disorder affecting 3%–11% of children and frequently persists into adulthood [11–14]. The main symptoms of ADHD include an ongoing inability to sustain attention, deficits in inhibition, hyperactive behavior, and impulsivity [15–17]. Features of narcolepsy, such as EDS and nocturnal sleep disturbance, can impair children's ability to pay attention, learn and conduct [18]. It is unknown whether a high incidence of ADHD symptoms in narcolepsy patients represents true comorbidity with ADHD or ADHD-like symptomatology secondary to narcolepsy. To clarify this has important implications.

Furthermore, a number of studies have examined depression, anxiety, quality of life and executive function in narcolepsy patients compared with healthy controls or patients with other diseases [5,19–22]; however, few studies have explored the mood, quality of life and executive function between narcolepsy patients with and without ADHD symptoms.

Although the pathophysiological mechanisms shared by narcolepsy and ADHD are not yet well known, both disorders can be treated with methylphenidate [23,24]. The National Institute for Health and Care Excellence (NICE) guidelines for ADHD recommend that the methylphenidate can be increased to 0.7 mg/kg per dose up to three times a day, or a total daily dose of 2.1 mg/kg/day (or an equivalent dose of modified-release methylphenidate) [25]. For the treatment of narcolepsy, as base preparation, immediate release (5–10 mg) can be helpful to alleviate daytime sleepiness in hypersomnia, when using long-acting formulations of methylphenidate typically 20–40 mg/day [26]. Methylphenidate Hydrochloride Extended-release tablets (ER-MPH) is recommended as a first-line medication for ADHD in China [27], and it is the only available medication for off-label use in childhood narcolepsy in China. The dose recommended is between 18 mg/day to 54 mg/day. The pathophysiological mechanisms of narcolepsy remain unclear, comorbid ADHD may suggest shared underlying mechanisms between these two disorders and help to identify new genetic or molecular targets for narcolepsy treatment.

In this study, we hypothesize that NT1 patients with ADHD symptoms have worse mood, quality of life and executive function compared with NT1 patients without ADHD symptoms, and methylphenidate treatment may benefit both sleepiness and ADHD symptoms. The aims were to investigate the prevalence of ADHD symptoms in a large sample of juvenile NT1 patients, and to explore whether ADHD symptoms worsen mood, quality of life, and executive function in NT1 patients and the therapeutic role of methylphenidate.

2. Methods

2.1. Participants

The study was conducted from February 2011 to July 2013. A total of 267 children (younger than 12 years old) and adolescents (12–18 years old) with narcolepsy type 1 (NT1) were recruited. All patients underwent a medical interview by the sleep specialist using Stanford Sleep Inventory (SSI) [28,29]. Patients were systematically evaluated for clinical parameters, including disease onset, disease duration and general demographic information. Polysomnogram (PSG) followed by multiple sleep latency tests (MSLTs) and human leukocyte antigen (HLA) typing were conducted. Patients with NT1 were diagnosed according to the ICSD-2 criteria [30], including (1) complaints of excessive daytime sleepiness (EDS) for at least 3 months; (2) presence of clear-cut cataplexy and a mean sleep latency $\leq$ 8 min with $\geq$ 2 sleep onset rapid eye movement periods (SOREMPs) during MSLTs (REM onset within 15 min of sleep onset during preceding nocturnal PSG may replace one of the SOREMPs during the MSLTs). Written informed consent from both the participants and parents of minors/legal guardians was obtained for the study. This study was approved by the institutional review board of Peking University People's Hospital (Number: 2011–86). The recruitment of the participants was shown in Fig. 1.

2.2. ADHD evaluation

All participants were evaluated in the clinical interview by an experienced clinical psychologist according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria [31]. The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid) was also used to assess comorbidities during the interview. Symptoms of ADHD were scored by parents using the ADHD rating scale (ADHD-RS) [32], and the Chinese version of the ADHD-RS was validated [33,34]. The clinically significant ADHD symptoms were categorized into three subtypes, i.e., inattentive only (ADHD-I), hyperactive-impulsive only (ADHD-H) and inattentive combined with hyperactive-impulsive symptoms (ADHD-C).

2.3. Psychological questionnaires

A modified Chinese version of the Depression Self-Rating Scale for Children (DSRS-C) [35–37], which has a score range of 0–36, was used to assess children's and adolescents' depressive symptoms. Higher DSRS-C scores indicate higher depression levels. Symptoms of anxiety disorders were measured using Screen for Child Anxiety Related Emotional Disorders (SCARED) [38–40], a 41-item self-report questionnaire including five factors that parallel the DSM-IV classification of anxiety disorders: panic/somatic, generalized anxiety, separation anxiety, social phobia, and school phobia. Higher SCARED scores indicate higher anxiety level. Impulsive behaviors were evaluated using the Barratt Impulsiveness Scale (BIS) [41,42], in which participants reported the frequency of different behaviors. The total score ranges from 30 to 120, with higher scores meaning higher impulse levels.

Executive functions were assessed using parent ratings of a preschool version of the Behavior Rating Inventory of Executive Function (BRIEF) [43]. The BRIEF consists of 86 items and was developed to capture an individual's view of his/her child's purposeful, goal-directed, problem-solving behaviors. Ratings are summed across items in two dimensions and eight clinical scales, i.e., Behavioral Regulation Index (BRI): Inhibit, Shift and Emotional Control; Metacognition Index (MI): Plan/Organize, Initiate, Working Memory, Organization of Materials and Monitor. A Chinese BRIEF-P [44], translated and validated by Dr Qian Ying at the Institute of Mental Health of Peking University, was used in this study. We computed “inconsistent”, “negative evaluation rate” and “infrequency rate” in the BRIEF primary score and eliminated

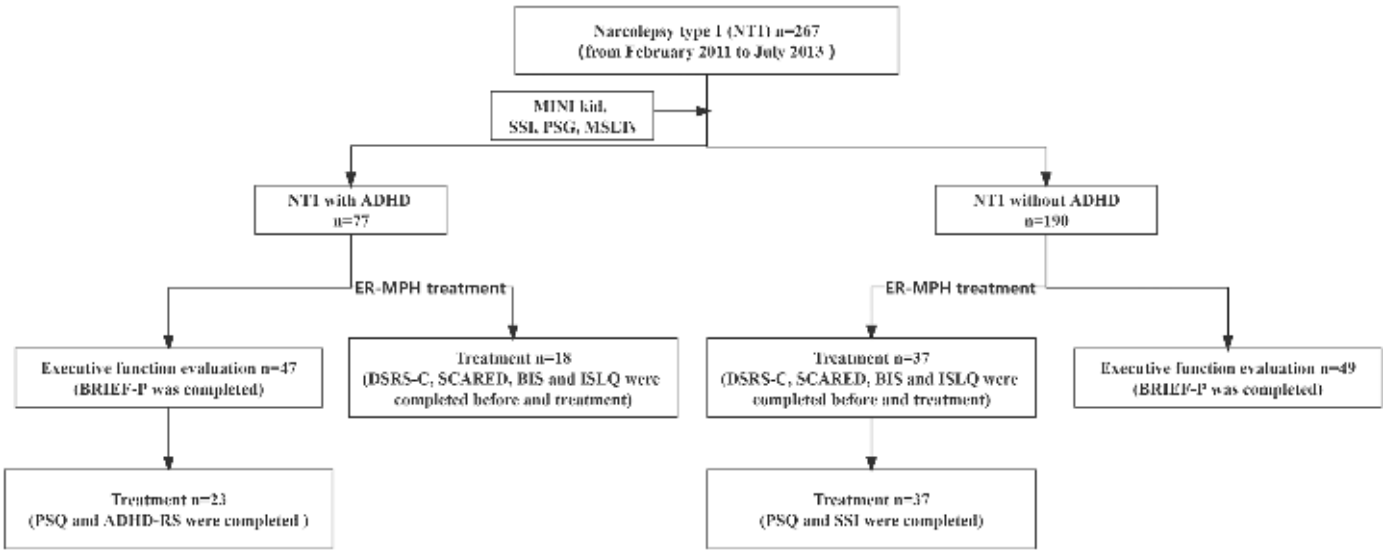

Fig. 1. Flow diagram of the participants' recruitment
NT1 : Narcolepsy type 1; MINI Kid : Mini International Neuropsychiatric Interview for Children and Adolescents; SSI : Stanford Sleep Inventory; PSG : Polysomnogram; MSLTs : Multiple Sleep Latency Tests; ADHD : Attention-Deficit/Hyperactivity Disorder; ER-MPH : Methylphenidate Hydrochloride Extended-release tablets; BRIEF-P: Behavior Rating Inventory of Executive Function-Parent version; DSRS-C: Chinese version of Depression Self-resting Scale for Children; SCARED : Screening for Child Anxiety-related Emotional Disorders; BIS : Barratt Impulsiveness Scale; ISLQ : Inventory of Subjective Life Quality; PSQ : Pediatric Sleep Questionnaire; ADHD-RS : Attention-Deficit/Hyperactivity Disorder Rating Scale.

unqualified questionnaires. The higher the score, the more severely impaired the executive function.

Health-related quality of life was assessed using a self-report questionnaire named the Inventory of Subjective Life Quality for Chinese children and adolescents (ISLQ) [45]. The ISLQ consists of 52 items covering family life, partner contact, school life, living environment, self-cognition, depression experience, anxiety experience and body experience emotion. Higher ISLQ scores indicate higher quality of life.

2.4. Methylphenidate treatment

In this study, the total daily dose of ER-MPH was 9–18 mg once a day according to the age and bodyweight of the children. NT1 patients with comorbid ADHD symptoms received 16 weeks of treatment with methylphenidate hydrochloride controlled-release (ER-MPH) tablets (9–18 mg). After 16 weeks of treatment, we performed telephone interviews to evaluate narcolepsy and ADHD symptoms (ADHD-RS). The sleep and narcolepsy symptoms were evaluated by SSI and the Pediatric Sleep Questionnaire (PSQ) [46]. The SSI is a validated questionnaire predictive of cataplexy, it also evaluates the presence and severity of various other narcolepsy symptoms such as sleepiness, napping, disturbed nocturnal sleep, sleep paralysis, and hypnagogic hallucinations (see http://med.stanford.edu/school/Psychiatry/narcolepsy/). The PSQ is a 22-item tool consisting of 4 factors: breathing, sleepiness, behavior, and others. Each item was answered yes, no or unknown, with a yes score of 1. Higher scores indicate more severe symptoms. The Chinese version of the PSQ was reported to have good validation and reliability [47,48].

2.5. Statistical analysis

We used SPSS 20.0 (SPSS Inc., Chicago, Ill., USA) to perform statistical analysis. Categorical variables for the sample are presented as percentages, and quantitative variables are presented as medians with ranges. Statistical analysis of the characteristics of participants belonging to different groups was performed by independent-samples *t*-test, and the results of the same sample before and after treatment were performed by paired-samples t-tests. $p<0.05$ was considered as statistically significant.

3. Results

3.1. Prevalence of ADHD symptoms in children and adolescents with NT1

28.8% of NT1 (77/267) patients manifested core ADHD symptoms, 94.8% of whom (73/77) fell into the ADHD-I category and 5.2% (4/77) met the ADHD-C criteria. Of these 77 patients, 48.1% (37/77) had ADHD symptoms before the diagnosis of NT1, 19.5% (15/77) at the time of diagnosis, and 32.5% (25/77) after diagnosis.

3.2. Demographics and NT1 associated features

Table 1 depicts the demographics and NT1-associated features of the participants. The demographic components between NT1 patients with and without ADHD were comparable, with an average age of 10 years old and mainly male. Patients in both groups had early-onset narcolepsy and suffered from cataplexy and excessive daytime sleepiness. A higher body-mass index (BMI) was seen in NT1 patients with ADHD. No differences were found in the prevalence of hallucinations, sleep paralysis or disturbed nocturnal sleep.

3.3. Mood and life quality assessment

Compared with NT1 patients without ADHD symptoms, NT1 patients with ADHD symptoms tended to have more anxiety symptoms (29.9 ± 12.1 vs 23.2 ± 9.4, $p<0.05$), higher impulsivity reflected by BIS scores (64.4 ± 13.4 vs 57.7 ± 10.7, $p<0.05$) and lower quality of life (111.9 ± 9.9 vs 119.2 ± 11.1, $p<0.05$) before ER-MPH treatment (Table 2). NT1 patients with ADHD symptoms tended to have more anxiety symptoms (29.9 ± 11.1 vs 24.0 ± 9.3, $p<0.05$)

Table 1
Demographics and NT1 associated features of participants.

Characteristics	NT1 with ADHD	NT1 without ADHD	P value
Age (y)	10.0 ± 2.8 (77)	10.4 ± 3.4 (190)	0.45
BMI	23.2 ± 4.4 (76)	22.1 ± 4.6 (186)	0.03
Gender (%, male)	70.1% (54/77))	73.7% (140/190)	0.51
ADHD onset age (y)	7.3 ± 0.7 (77)	N/A	N/A
NT1 onset age (y)	7.9 ± 2.4 (77)	7.9 ± 2.2 (190)	0.93
HLA-DQB1*06:02 (%)	100%	100%	N/A
Cataplexy (%)	100%	100%	N/A
Hallucination (%)	54.0% (34/63)	41.7% (66/158)	0.15
Sleep paralysis (%)	25.4% (16/63)	28.8% (45/156)	0.74
Disturbed sleep (%)	88.5% (54/61)	87.7% (135/154)	1.00
AHI (times/hour)	1.2 ± 1.7 (68)	1.3 ± 2.6 (175)	0.83
MSLT-sleep latency (min)	3.6 ± 3.7 (77)	3.3 ± 2.8 (190)	0.62
MSLT-SOREM times	4.1 ± 1.4 (77)	4.2 ± 1.1 (190)	0.71

NT1 : Narcolepsy Type 1, BMI : Body Mass Index, ADHD : Attention-Deficit/Hyperactivity Disorder, PSQ : Pediatric Sleep Questionnaire, AHI : Apnea-Hypopnea Index, MSLT : Multiple Sleep Latency Test, SOREM: Sleep Onset Rapid Eye Movement Period.

and lower quality of life (112.3 ± 9.5 vs 121.3 ± 11.3, p<0.05) than NT1 patients without ADHD after ER-MPH treatment. Moreover, in the NT1 patients without ADHD group, the results showed more depression symptoms (19.5 ± 3.4 vs 21.1 ± 3.5, p<0.05), anxiety symptoms (19.5 ± 3.4 vs 21.1 ± 3.5, p<0.05) and high quality of life (119.2 ± 11.1 vs 121.3 ± 11.3, p<0.05) after ER-MPH treatment.

3.4. Executive function evaluation

Parent ratings of BRIEF (BRIEF-P) were used to evaluate executive functions in children and adolescent NT1 patients with or without ADHD. NT1 juveniles with ADHD comorbidity scored higher on all 8 BRIEF subscales and two broader indexes than those without ADHD, suggesting that comorbid ADHD worsened cognitive processes, emotional responses and behavioral actions (Table 3).

3.5. Effect of methylphenidate treatment

Sixty NT1 patients completed 16 weeks of ER-MPH treatment (9–18 mg/d). The PSQ scores dropped from 16.7±2.1 before treatment to 13.5 ±1.9 after treatment (p<0.001) in NT1 patients with ADHD symptoms, indicating a significant reduction in daytime sleepiness. On the contrary, no improvement was seen in core ADHD symptoms as evaluated by ADHD-RS (25.3 ± 9.1 vs 26.4 ± 8.9, p>0.05) after ER-MPH treatment at this dose.

4. Discussion

The major findings in this study include that: (1) Chinese Children with NT1 has high prevalence (28.8%) of ADHD, majorly inattention subtype. (2) ADHD symptoms worsen mood, quality of life, and executive function in NT1 patients. (3) Routine dose of ER-MPH in clinical practice can improve sleepiness as expected. However, no improvement in ADHD symptoms was observed after ER-MPH treatment.

Our study demonstrated that 28.5% of NT1 patients suffer from ADHD symptomatology, which was larger than children and adolescents with narcolepsy comorbid with ADHD (26.3%, 10/38) in western Sweden [9] and ADHD symptoms in children and adolescents with narcolepsy (23.1%, 18/78) in four French national reference centers for narcolepsy [7]. Since the neurological pathways associated with attention and wake sleep are located closely in the central nervous system, it is not surprising to see a high incidence of these two comorbidities. A recent systematic review of the prevalence of ADHD symptoms in narcolepsy reported that the two studies observed a pooled prevalence of ADHD symptoms in narcolepsy of 25.0% [10]. Two other studies (30.6%, 11/36; 44.4%, 11/25) [49,50] exhibited a pooled prevalence of ADHD symptoms in narcolepsy of 36.4% [10]. A retrospective survey showed that approximately 37.9% (61/161) of adults with narcolepsy had self-reported childhood ADHD symptomatology [8]. The differences in the prevalence of ADHD symptoms among patients with narcolepsy could be explained primarily by the methodological characteristics of the studies. In addition, the prevalence of ADHD symptoms in narcolepsy far exceeded the DSM-IV ADHD prevalence in children and adolescent populations (5.9%–7.1%) [51].

Furthermore, the result of ADHD subtypes was mostly inattention type (94.8%, 73/77) in this study. Evidence had supported that ADHD-I was the predominant subtype in China among college students [52], adults [53], and children and adolescents [54]. Similarly, Szakács et al. [9] reported that ten of 38 narcolepsy patients were diagnosed with ADHD and all of them (ten) were inattention type. In summary, a high prevalence of ADHD symptoms in narcolepsy, mostly inattention type, was consistent with previous studies.

We compared mood and quality of life in a clinical sample of NT1 patients with or without ADHD symptoms before and after ER-MPH treatment. We found that compared with NT1 patients without ADHD symptoms, NT1 patients with ADHD symptoms suffered from more anxiety, higher impulsivity and lower quality of life before ER-MPH treatment, and NT1 patients with ADHD symptoms still had more anxiety symptoms and lower quality of life after ER-MPH treatment. Impairment quality of life was already reported in narcolepsy patients compared with healthy controls [5,19,21,55,56] but without taking the impact of ADHD symptoms on the quality of life of patients with narcolepsy into account. These findings showed that comorbid ADHD symptoms may further impair the quality of life of patients with narcolepsy.

Moreover, previous studies showed that narcolepsy have a high comorbidity for psychiatric disorders, such as depression [57–59], anxiety [2,20] and eating disorders [2,60]. Our study showed that NT1 patients with ADHD symptoms suffered from more severe

Table 2
Mood and life quality assessment in pre and post ER-MPH treatment NT1 patients.

	NT1 with ADHD		NT1 without ADHD	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
DSRS-C	20.4 ± 3.9 (18)	20.8 ± 3.7 (18)	19.5 ± 3.4 (35)	21.1 ± 3.5 (35)*
SCARED	29.9 ± 12.1 (18)	29.9 ± 11.1 (18)	23.2 ± 9.4 (35)[a]	24.0 ± 9.3 (35)[b,*]
BIS	64.4 ± 13.4 (18)	64.1± 13.1 (18)	57.7 ± 10.7 (37)[a]	58.6 ± 11.9 (37)
ISLQ	111.9 ± 9.9 (18)	112.3 ± 9.5 (18)	119.2 ± 11.1 (34)[a]	121.3 ± 11.3 (34)[b,*]

ER-MPH: Methylphenidate Hydrochloride Extended-release tablets, NT1: Narcolepsy Type 1, DSRS-C : Chinese version of Depression Self-Rating Scale for Children, SCARED :Screen for Child Anxiety Related Emotional Disorders, BIS : Barratt Impulsiveness Scale, ISLQ: Inventory of Subjective Life Quality.
a, p<0.05 in the NT1 with ADHD group compared with the NT1 without ADHD group before treatment.
b, p<0.05 in the NT1 with ADHD group compared with the NT1 without ADHD group after treatment.
*, p<0.05 before treatment compared with after treatment in the NT1 without ADHD group (paired T test).

Table 3
Executive function evaluation in NT1with and without ADHD.

Factors in BRIEF-P	NT1 with ADHD (N = 47)	NT1 without ADHD (N = 49)	t	p value
Inhibit	18.1 ± 4.0	13.5 ± 3.0	−6.373	<0.001
Shift	14.4 ± 2.8	12.0 ± 3.5	−3.631	<0.001
Emotional control	17.6 ± 4.1	15.0 ± 3.1	−3.423	0.001
Monitor	18.2 ± 3.9	13.4 ± 2.5	−7.156	<0.001
Initiate	15.9 ± 2.8	13.0 ± 3.3	−4.622	<0.001
Working memory	22.4 ± 4.4	15.2 ± 3.4	−8.930	<0.001
Plan/Organize	24.1 ± 5.2	18.7 ± 5.0	−5.173	<0.001
Organization of Materials	14.3 ± 2.5	10.3 ± 2.4	−7.911	<0.001
Total	173.5 ± 28.5	133.5 ± 27.6	−6.987	<0.001
Regulation index	50.0 ± 9.7	40.6 ± 8.0	−5.184	<0.001
Metacognition index	94.9 ± 16.3	70.7 ± 15.1	−7.550	<0.001

NT1: Narcolepsy Type 1, BRIFE-P : parents' ratings of the Behavior Rating Inventory of Executive Function.

anxiety and lower quality of life than NT1 patients without ADHD symptoms both before treatment and after treatment. This finding revealed that comorbid ADHD symptoms further spurred mood and psychological disorders in NT1 patients. Despite similar objective sleep parameters (PSG-measured AHI, MSLT-sleep latency, MSLT-SOREM times), more severe mood disorders were seen in NT1 with ADHD; thus, accurate recognition of ADHD in children with NT1 could allow for the introduction of appropriate ADHD treatments that could, in turn, reduce psychosocial impairment and enhance the quality of life of such children and adolescents.

It is worth noting that NT1 patients with ADHD symptoms had a high level of impulsivity compared with NT1 patients without ADHD symptoms before treatment (Table 2). One study investigating the effect of psychostimulants on impulsivity in narcolepsy with cataplexy showed that no difference was found for impulsivity among a drug-free group, treated group and healthy control group [61]. These findings suggested that NT1 patients might have normal levels of impulsivity, while ADHD symptoms exacerbate this in NT1 patients.

The results of executive function evaluation between the two groups showed that NT1 with ADHD worsened executive function. Previous studies assessing attention and executive function in patients with narcolepsy showed deficits in tests of executive function versus healthy controls [22,62,63], and executive functions (in particular, verbal fluency and resistance to stimuli interference) were one of the most impaired cognitive functions in NT1 patients [64]. Similarly, there were studies showing impaired executive function in patients with ADHD [65–68], as ADHD core symptoms (inattention and/or hyperactivity-impulsivity) were linked to reduced executive functions [69,70]. It is reasonable that NT1 patients with ADHD symptoms exhibited worse executive function.

In the NT1 without ADHD symptoms group, the mood was worse after treatment, while the quality of life was better in our study (Table 3). Methylphenidate is a stimulant medication exerting an effect on dopaminergic and noradrenergic systems and has been used to treat a variety of diseases, such as ADHD disorders, affective disorders and narcolepsy. There is controversy in regard to the potential role of methylphenidate in treating patients with depression [23]. Of note, the findings from this study showed that low dose of ER-MPH may increase anxiety and depression. Further studies are warranted focusing on the role of methylphenidate in improving emotion among patients with narcolepsy, especially combination with other anti-cataplexy medication such as tricycle antidepression medications. Our results showed ER-MPH treatment was associated with improvement in quality of life in NT1 without ADHD symptoms groups. Similarly, Becker et al. revealed that modafinil significantly improved the quality of life in patients with narcolepsy [71].

In the NT1 with ADHD symptoms group, sleepiness symptoms improved after treatment, while little improvement was found in ADHD symptoms (Table 4). Several studies suggest that methylphenidate reduces sleepiness in narcolepsy [23], which was also confirmed in our study. ER-MPH may be limited to improve cataplexy and DNS, which were both important symptoms of NT1. The typical cataplexy attack may mimic ADHD, and sleep disturbances and daytime sleepiness are also found in ADHD [72,73]. There are overlapping clinical features of narcolepsy and ADHD, adding medications treatment for cataplexy and DNS may be helpful to improve. Concerning lack of response for ADHD symptoms after treatment, it may be related to the dose of methylphenidate. A meta-regression analysis showed that methylphenidate improved ADHD symptoms in adults in a dose-dependent fashion [74]. Therefore, the low dose of ER-MPH (9–18 mg/day) works for EDS in narcolepsy but not enough to improve ADHD symptoms in this study. In the cooccurrence of ADHD and NT1, different treatment strategies may be considered, such as increasing drug dosages and enhancing monitoring and behavior training. Future research is warranted to elucidate the link between ADHD and narcolepsy, which will define a scientific basis for more personalized treatment. Higher BMI was observed in NT1 patients with ADHD in this study. The key for NT1 was the loss of orexin/hypocretin neurons, and therefore low levels of orexin in the cerebrospinal fluid, which leads weight gain in both narcoleptic animals [75] and human [76–78]. On the other hand, the prevalence of ADHD in the population with a BMI≥30 may be as high as 27.4%, whereas in the general population it stands at about 3%–4% [79]. In turn, adults and children with ADHD have, respectively, a 70% and 40% increased risk of developing obesity [80]. Heterogeneous

Table 4
Effect of methylphenidate treatment in NT1 patients (N = 60).

	Before treatment	After treatment	t	p value
PSQ (n = 23)	16.7 ± 2.1	13.5 ± 1.9	6.637	<0.001
ADHD-RS (n =23)	25.3 ± 9.1	26.4 ± 8.9	−0.664	0.514
PSQ no-ADHD [a] (n = 37)	17.4 ± 1.6	14.9 ± 1.4	10.159	<0.001

PSQ : Pediatric Sleep Questionnaire, ADHD-RS : Attention-Deficit/Hyperactivity Disorder Rating Scale.
[a] The scores of PSQ before and after treatment in NT1 patients without ADHD symptoms.

pathogenetic pathways may exist to explain the connection between these two conditions. Emerging medication focusing on orexin/hypocretin system such as orexin-receptor agonists (especially receptor 2) may be promising candidates for treating narcolepsy in the future [81–83], where this treatment would benefit ADHD in NT1 remain to be studied.

Decreased attention in NT1 patients may result from their drowsiness during the day, but our study favors ADHD symptoms observed in NT1 youths who present true comorbidities other than secondary changes for three main reasons: 1) ADHD symptoms proceed narcolepsy onset in approximately half of the NT1 patients with ADHD symptoms; 2) neither age of onset, objective sleepiness nor the frequency of cataplexy, hallucination, sleep paralysis differed between NT1 with or without ADHD symptoms; thus, ADHD is not due to more severe narcolepsy; and 3) a low dose of methylphenidate, which significantly improved daytime sleepiness, had no effect on core ADHD symptoms.

Our study also has limitations. First, the cross-sectional design cannot demonstrate a causal relationship between narcolepsy and ADHD but only compares findings between the NT1 with or without ADHD groups. Second, the absence of executive function evaluation after treatment in the two groups limits the comparison with before treatment to disentangle the effect of methylphenidate treatment on executive functions.

In conclusion, a high prevalence of ADHD symptoms in children and adolescents with NT1 was found. Comorbid ADHD symptoms in NT1 patients were associated with increased levels of mood disorders, lower quality of life and worse executive functions. MPH treatments could reduce narcolepsy symptoms but not ADHD symptoms in NT1 patients with ADHD, suggesting that new treatment strategies are needed for this group of patients.

Declaration of competing interest

The authors declare that there are no competing interests.

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