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High prevalence of ADHD symptoms in unmedicated youths with post-traumatic stress disorder type 1

Berit Hjelde Hansen¹, Hilde T Juvodden^{1,2}, Sebjørg Hesla Nordstrand^{2,3},
Rannveig Viste^{1,2}, Per M Thorsby⁴, David Swanson⁵, Kristian B Nilsen⁶,
Næerland^{1,2}, Stine Knudsen-Heier¹

1 Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias, of Rare Disorders, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

2 Institute of Clinical Medicine, University of Oslo, Norway

3 Department of Pediatrics, Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Ullevål Hospital, Norway

4 Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, Aker Hospital, Oslo, Norway

5 Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital

6 Department of Neurology, Section for Clinical Neurophysiology, Oslo University Hospital, Oslo, Norway

Corresponding author: Berit Hjelde Hansen, Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias, P.B. 4956, Nydalen, 0424 Oslo, Norway

E-mail: bihn@ous-hf.no

Abstract

Objectives To characterize attention deficit-hyperactivity disorder (ADHD) symptoms in unmedicated post-H1N1 narcolepsy type 1 (NT1) youths, and explore association between ADHD symptoms and the narcolepsy phenotype.

Methods Fifty consecutively enrolled post-H1N1 NT1 youths (7-20 years, 62% female, HLA-DQB1*06:02-positive, 98 % CSF hypocretin-1 deficient, 88% vaccinated) were assessed after two weeks off medication for ADHD (ADHD diagnosis pre/post-narcolepsy, parent-rated ADHD symptoms) and narcolepsy-phenotyped (semi-structured interview, Sleep Questionnaire, Epworth Sleepiness Scale, polysomnography (PSG), Multiple Latency Test (MSLT)).

Results 26 (52%) and 15 (30%) of participants had ADHD symptoms above and below the clinical significant cut-off, respectively, while 9 (18%) had no ADHD symptoms. Higher scores were found for ADHD total score (mean (SD), 17.9 (9.5)) and ADHD subscores (inattention score, 11.0 (6.3); hyperactive/impulsivity score, 6.9 (4.7)). These were significantly higher than previously reported in a mainly medicated narcolepsy cohort ($p < 0.0001$). Age and disease duration did not influence scores. Two participants (4%) had ADHD symptoms prior to narcolepsy onset. ADHD symptoms were correlated with parent-rated, but not patient rated ESS scores, objective sleepiness (mean sleep latency), sleep fragmentation (sleep stage shift index, awakening index), or CSF hypocretin-1 level.

Conclusion Comorbid ADHD symptoms were more prevalent in unmedicated post-

narcolepsy sleep/wake phenotype characteristics, indicating that the ADHD symptoms are not a direct consequence of disturbed sleep or daytime sleepiness.

Keywords: ADHD symptoms, narcolepsy, H1N1

Abbreviations:

ADHD Attention Deficit- Hyperactivity Disorder

NT1 narcolepsy type 1

NT2 narcolepsy type 2

PSG polysomnography

MSLT Multiple Sleep Latency Test

CSF cerebrospinal fluid

Hcrt-1 hypocretin-1

ICSD-3 International Classification of Sleep Disorders 3rd version

SDB sleep disordered breathing

PLM periodic limb movement

AASM American Academy of Sleep Medicine

ADHD RS ADHD rating scale

TST total sleep time

SSQ Stanford Sleep Questionnaire

ESS Epworth Sleepiness Scale

CV coefficient of variation

SD standard deviation

ASEBA Achenbach System of Empirically Based Assessment

CBCL Child Behavior Checklist

ASR Adult Self Report

HH hypnagogic hallucinations

SP sleep paralysis

AHI apnea/hypopnea index

SL sleep latency

MWT maintenance of wakefulness test

RLS restless legs syndrome

REM rapid eye movement

SSRI selective serotonin reuptake inhibitor

1. INTRODUCTION

Narcolepsy is a chronic neurological disorder affecting the sleep-wake and muscle regulatory systems in the brain (1). Core narcolepsy symptoms consist of excessive sleepiness, disrupted night sleep and sleep fragmentation, cataplexy (sudden loss of tone typically triggered by strong emotions), sleep paralysis, and hypnagogic and hypnopompic hallucinations. According to the 3rd edition of the International Classification of Sleep Disorders (ICSD-3) (2), narcolepsy type 1 (NT1) is differentiated from narcolepsy type 2 (NT2) by the presence of cataplexy and/or a low level of the neuropeptide hypocretin-1 in the cerebrospinal fluid (CSF Hcrt-1 levels). The hypocretin-producing cells in the hypothalamus project widely in the brain and strongly to the brain stem and thalamus, producing an excitatory effect on wake- and arousal-promoting nuclei, including those involved in noradrenergic and dopaminergic transmission (3). Destruction of hypocretin-producing neurons in the hypothalamus is considered a key pathophysiological pathway in NT1 (1). The prevalence of sporadic narcolepsy is estimated to be 25–50 cases per 100,000 individuals (4, 5). Following the 2009 H1N1 epidemic and vaccination campaign with the Pandemrix® vaccine, there was an abrupt increase in the incidence of NT1 in Norway and other countries (6-8).

The neurodevelopmental disorder Attention Deficit Hyperactivity Disorder (ADHD) is characterized by symptoms of inattention, impulsivity and hyperactivity. These symptoms, and especially so of inattention, are frequently reported in adults and children with narcolepsy (9-12), and it is associated with reduced quality of life, academic failure

pathophysiological mechanism (15). Sleep disturbances are a frequent comorbidity (16-18) and may precipitate and aggravate the ADHD symptoms (19, 20). Multiple dysfunctions may underpin the behavioral symptoms of ADHD, including difficult sustained attention, response inhibition, working memory, and executive functions necessary for attention regulation, planning and execution of tasks, self-regulatory monitoring (19, 21). Gender and age trends indicate that symptoms are more frequent in boys than in girls, and that ADHD symptom scores are higher in younger than in older children (22).

The exact "true" prevalence of ADHD symptoms in pediatric narcolepsy is unknown as the majority of young people considered in the previous studies were taking some medication for their narcolepsy at the time their ADHD symptoms were measured (12). Many of these medications are the treatments of choice for ADHD (23). One study reported ADHD symptoms above the clinical cut-off in almost 20% of a sample of children with NT1 (87% sporadic, 67.1 % were taking medication, ADHD assessed in 61 children) and in another study of 38 children with narcolepsy (18.4 % sporadic, 94.7% were taking medication, ADHD scores assessed in 32 children) more than one in four met criteria for ADHD diagnosis (10). Finally, an Italian study reported higher ADHD scores in children with narcolepsy (72% medicated) compared with controls (12).

The mechanisms driving the high levels of occurrence of ADHD symptoms in pediatric narcolepsy are unknown. One explanation may be that pre-existing ADHD represents a vulnerability for the development of narcolepsy in the face of particular environmental triggers. For instance,

narcolepsy are due to a low level of Hcrt-1 (9, 25), or to be a consequence of sleep fragmentation (9, 20, 25, 26). However, empirical support for these explanations is scarce. Associations between ADHD symptoms and CSF Hcrt-1 levels in narcolepsy have not been extensively studied. One pediatric, and largely sporadic study reported no significant association, although very few had their CSF Hcrt-1 levels measured (9), and two sporadic adult populations did not report any significant difference in ADHD symptoms between NT1 (low CSF Hcrt-1 levels) and NT2 (normal CSF Hcrt-1 levels) (26). Results are not consistent regarding the associations between ADHD symptoms and daytime sleepiness. One pediatric study reported an association between ADHD symptoms and subjective daytime sleepiness, while no associations were found between ADHD symptoms and objective measures of sleepiness. However, the conclusions were limited because the sample was mostly medicated and there was an average of 1.2 years between ADHD symptom assessment and the sleep investigations (9). No significant correlations between ADHD symptoms and subjective or objective daytime sleepiness were found in unmedicated individuals with a primary central hypersomnolence disorder (26), while a positive correlation between ADHD scores and subjective daytime sleepiness was reported from 21 unmedicated NT1 (27). To our knowledge, associations between ADHD symptoms and measures of sleep fragmentation have not previously been examined in the context of narcolepsy.

The aim of this study is to characterize ADHD symptoms in a sample of unmedicated H1N1 NT1 young people, defined as youths with narcolepsy type 1 with debut after age 10.

objective narcolepsy phenotypic features (CSF Hcrt-1 levels, subjectively reported sleepiness, multiple sleep latency test (MSLT) mean sleep latency, polysomnographic sleep fragmentation). As sleep-disordered breathing (SDB) and periodic limb movements (PLM) symptoms have both been associated with ADHD symptomatology (16, 17) we wanted to adjust for possible associations between ADHD symptoms and PSG measures of SDB and PLM symptoms. Lastly, we wanted to explore whether ADHD symptomatology in narcolepsy is due to ADHD existing prior to narcolepsy onset, or family aggregation of or other neurodevelopmental disorders, likely to be associated with high levels of ADHD symptoms even in the absence of a formal ADHD diagnosis (28).

We hypothesized that: our sample of unmedicated post-H1N1 NT1 youths would have higher ADHD symptom scores; inattentive symptoms in our group would be significantly more frequent than hyperactive/impulsive symptoms; and ADHD scores would be significantly higher than previously reported in mainly medicated youths with narcolepsy. We had no *a priori* hypothesis about any association of ADHD symptoms with a pre-existing AI diagnosis or family aggregation of neurodevelopmental disorders, CSF Hcrt-1 levels, or measures of daytime sleepiness, or sleep fragmentation.

2. METHODS

2.1 Participants

Following the increase in narcolepsy incidence in Norway after the 2009 H1N1 epidemic, we initiated a research project at the Norwegian Centre of Expertise for Neurodevelopmental Disorders (NCE) in 2010. The NCE is a national center for research and clinical work in the field of neurodevelopmental disorders, and is part of the Norwegian Centre of Expertise for Neurodevelopmental Disorders (NCE).

and Care Services to register and follow up all patients with narcolepsy onset after 2009 in Norway, irrespective of their vaccination status.

Between February 2015 and June 2017, after obtaining written consent, 63 NT1 (years old) were consecutively enrolled at our center. We have previously reported population partially overlapping our study population. The large majority of participants had previously been treated, hence were not medication naïve. All participants were instructed to be unmedicated with their narcolepsy medication and all other medication affecting sleep for two weeks prior to inclusion in accordance with recommendations from the American Academy of Sleep Medicine (AASM) (29). Furthermore, participants on antiepileptic medication were instructed to taper these off over 1-2 weeks (dependent on dosage) prior to the two unmedicated weeks. All participants complied with these instructions, except one who was allowed to remain on venlafaxine due to severe depression.

The majority - 34/50 (68%) - of participants attended school in the unmedicated period with some adjustments. A total of 14/50 (28%) were included during a school vacation period and 2/50 (4%) did not attend school in the two week period prior to assessment. Comparison between the group attending school versus those included in vacation or not attending school of ADHD rating scale (RS) total, inattentive, and hyperactive scores revealed no significant differences ($p=0.519$; $p=0.747$; $p=0.392$, respectively). Of the 63 youths (79.4%) had an ADHD (RS) provided by their parents. There were no significant differences in demographic or clinical sleep variables between the 13 participants that did not and did have a parentally assessed ADHD RS, except the 13-month

group with parental ADHD RS (mean (SD) TST, 6.5 (2.1) vs. 8.0 (1.0); $p = 0.005$). TI with no ADHD RS available were excluded from further analyses.

The study was approved by the Norwegian regional committees for medical and health research ethics (REK).

2.2 Procedure

Participants were instructed to wear an actigraph (Actiwatch Spectrum Plus, Phillips) 7 days before inclusion (e.g. during the unmedicated period). Following admission to the sleep center, semi-structured interviews, and questionnaires (Stanford Sleep Questionnaire, including the Epworth Sleepiness Scale (ESS) (patient- and parent-rated)) (30), an actigraph (parent-rated) were administered (31). Sleep investigations (PSG, MSLT) were conducted and blood samples taken to determine routine parameters and carry out HLA analysis. This was done in order to verify and validate the narcolepsy diagnosis according to the criteria and to provide a detailed description of the sleep phenotype as part of our specific assignment, and also to – for research and comparable purposes - ensure that the sleep investigations were performed with the same method for all participants. All underwent an overnight PSG followed by an MSLT with five 30-minute nap opportunities. Technical details of the PSG/MSLT procedure have been published previously (32). All sleep recordings were scored by two skilled sleep technicians/nurses, who scored the sleep stage and arousals events according to AASM criteria (33). The clinical and sleep parameters were evaluated by an experienced neurologist and sleep medicine expert (SKH) using the ICSD-3 criteria for narcolepsy diagnoses (2), including the verification of the NT1 diagnoses.

previously described (34). Limit of detection (LOD) was 20 pg/ml and limit of quantification (LOQ) 40 pg/ml where the coefficient of variation (CV) was 20%. At 109 pg/ml the method was 9%. Lumbar punctures for sampling CSF were performed at local hospital before (in 88 % of cases) or after study inclusion, in average 3.3 years (range 0.1 to 4.5 years) prior to inclusion or in average 0.3 years (range 0.08 to 0.4 years) after study assessment.

2.3 Measures

2.3.1 Present ADHD symptoms

ADHD symptoms were assessed by parental ratings of ADHD symptoms on the ADHD RS as occurring during the unmedicated period. The ADHD RS is a questionnaire measuring severity of the ADHD symptoms inattention, hyperactivity and impulsivity, and has been widely used in clinical populations, including in narcolepsy populations (9). It covers the 18 symptoms of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (31) rated on a scale comprising values of 0 (never), 1 (sometimes), 2 (often), and 3 (very often) (31) and for which good psychometric properties have been reported, including for the Norwegian version (35-37). Two subscale scores were calculated: the inattentive and hyperactivity/impulsivity scores, in addition to the ADHD total score, which is the sum of all 18 items. A higher score indicates more ADHD symptoms. There are no Norwegian population norms, and the presence of ADHD symptoms above the clinical cut-off was determined according to Danish population norms based on age- and gender-specific norms.

populations. A symptom of ADHD was considered to be present if the item was graded 2 or more. The youths were divided into three groups based on their ADHD symptom clinical scores (above the clinical cut-off according to the Danish group norms), ADHD symptoms (at least one item score of 2 or more, sum score below the clinical cut-off), ADHD symptoms (no item score above 1). Internal reliability of our sample was given by values of Cronbach's alpha of: 0.87, 0.89 and 0.75 for the total, inattentive and hyperactive/impulsivity scales, respectively. These results are comparable to those found in clinical ADHD populations (40).

2.3.2 ADHD diagnosis pre narcolepsy

ADHD diagnosis pre narcolepsy debut was assessed by patient chart review.

2.3.3 Family history of neurodevelopmental disorders

Family history of neurodevelopmental disorders was assessed by parental report in an interview with a questionnaire assessing familial occurrence of somatic and psychiatric disorders.

2.3.4 Other psychiatric symptoms

Our center has previously reported psychiatric symptoms in a sample of children with narcolepsy type 1 (41). In this study the Norwegian version of the Achenbach System of Empirically Based Assessment (ASEBA) was used; the parent-rated Child Behavior Checklist (CBCL) for age 6–18 years, and the corresponding Adult Self Report (ASR) for age

(anxious/depressed, withdrawn/depressed and somatic complaints) and an externalizing score (rule-breaking behavior, aggressive behavior and intrusive behavior (adult version only)). The other syndrome scales (thought problems, attention problems and somatic problems (child version only)), are used in conjunction with the internalizing and externalizing scores to derive a total score. Details on assessment and scoring have previously been published (41).

2.3.5 Subjective sleepiness

Subjective sleepiness was taken as that occurring during the unmedicated period (days 15-16), was assessed by self-report and parental report on the ESS, which yields scores ranging from 0 to 24. Scores of 11 or more are considered to indicate increased daytime sleepiness (45). ESS scores were available for all 50 participants with parental ADHD RS report, and parent-report of sleepiness was available for 43 (86%) of these participants.

2.3.6 Other core narcolepsy symptom

Cataplexy, hypnagogic hallucinations (HH), and sleep paralysis (SP) prevalences and frequencies were assessed at the end of the unmedicated period with the SSQ (3

2.3.7 Objective sleepiness and sleep fragmentation.

Mean MSLT SL was used as a measure of objective daytime sleepiness. Sleep fragmentation was assessed by the sleep stage shift index and awakening index (measured as the number of sleep stage shifts and awakenings divided by the TST respectively).

2.3.8 SDB and PLM

were measured by the apnea/hypopnea index (AHI) and periodic limb movement index (measured as the number of apnea/hypopnea events and periodic limb movements divided by the TST respectively).

2.4 Statistics

Data were analyzed with IBM SPSS version 23. Variables are summarized as frequency, the mean and SD, as appropriate. We tested the independence of pairs of categorical variables using chi-squared (χ^2) hypothesis tests, and for continuous variables, we used non-parametric tests (Mann-Whitney for independent samples, Wilcoxon's signed-rank for paired samples, Kruskal-Wallis for three or more samples, and Spearman's rho to measure correlation) (46), to prevent undue influence of outliers. We wanted to compare our results with previously reported ADHD scores from a sample of predominantly medicated children with NT1 (9), an ADHD sample (40), and a healthy control group (40). We first transformed the confidence intervals of the ADHD RS scores from the pediatric NT1 sample (A known for 61/86) to SDs using the formula: $SD = (C2 - m)/1.96$, where C2 is the upper quantile from a 95% confidence interval, and m is the group mean. We then compared group means with a two-sample t-test (<https://www.graphpad.com/quickcalcs/ttest1>). Multiple linear regression analyses, adjusted for age, gender, PLM index and AHI, were carried out to assess the association between ADHD total score, and scores for polysomnographic self-reported ESS, mean MSLT sleep latency (SL), sleep stage shift index, and awake

0.05 were considered statistically significant, unadjusted for multiple comparison exploratory nature of study.

3. RESULTS

3.1 Characteristics

Demographic and clinical data of the 50 participants, including sleep parameters summarized in Table 1. A majority (62%) of participants were female. CSF Hcrt-1 available for 49 (98%) of the participants with exact values known for 44 (88%) of Levels were further categorized into groups: < 40 pg/ml (n=23), 40-150 pg/ml (n= “low” (defined as “low” by the laboratory, but with no exact value available, n=5)

Please insert table 1 about here.

The self-reported and parent-reported ESS were significantly positively correlated ($r = 0.66, p < 0.001$). Ninety-eight percent of participants (49/50) were HLA DQB1*06. Mean MSLT SL was 3.3 minutes. Forty-six out of 50 participants were cataplectic. participants (8%) – all hypocretin deficient – were cataplexy negative. The majority of participants exhibited HH (82%) and SP (64%). There was an average of 14.4 sleep shifts / hour TST, and 2.5 awakenings / hour TST. The mean AHI was below the diagnostic threshold for sleep apnea both for adult (< 5 /hour TST) and pediatric criteria (< 1), while the PLM index was high (17.0/hour TST).

3.2 ADHD symptoms in NT1

26/50 (52%) of the young people had levels of ADHD symptoms above the cut-off to the Scandinavian (Danish) age- and gender-adjusted norms, 15 (30%) had one ADHD symptoms but with summed scores below the clinical range, and 9 (18%) had no ADHD symptoms, i.e. no item score greater than 1.

There was no significant difference in the proportions of the sexes among the three levels of ADHD symptom loads (ADHD clinical scores: 61.5% female; ADHD symptoms: 50% female; no ADHD symptoms: 44.4% female; $\chi^2 = 2.0$, $p = 0.362$). Youths with these levels of ADHD symptom loads did not differ with respect to *age at inclusion* (ADHD clinical scores: 14.7 years (3.0); ADHD symptoms: 16.2 years (3.0); no ADHD symptoms: 15.1 years (4.0); $p = 0.255$), *age at disease onset* (ADHD clinical scores: 9.3 years (3.1); ADHD symptoms: 11.3 (3.0); no ADHD symptoms: 9.5 years (3.3); $p = 0.205$), *disease duration* (ADHD clinical scores: 5.4 years (1.3); ADHD symptoms: 4.9 years (1.7); no ADHD symptoms: 4.6 years (1.5); $p = 0.217$), -or *age at H1N1 vaccination* (ADHD clinical scores: 8.5 years (3.1); ADHD symptoms: 9.8 years (3.3); no ADHD symptoms: 8.7 years (3.9); $p = 0.592$). There were few participants without ADHD symptoms ($n = 9$).

Mean (SD) ADHD RS scores were: total score, 17.9 (9.5); inattentive score, 11.0 (6.5); hyperactivity/impulsivity score: 6.9 (4.7). There were no differences in the ADHD subscale scores by gender; ADHD total score: girls 12.7 (7.8) versus boys 19.1 (11.0), $p = 0.484$; inattentive score: girls 10.5 (5.0) versus boys 11.7 (8.1), $p = 0.603$; hyperactive/impulsivity score: girls 6.6 (4.2) versus boys 7.4 (5.5), $p = 0.764$.

hyperactivity/impulsivity scores were not significantly correlated with age at inclusion, age at disease onset, age at vaccination, or disease duration (data not shown).

ADHD inattentive scores were significantly higher than hyperactivity/impulsivity scores (11.0 (6.3) versus 6.9 (4.7) respectively, $p < 0.001$).

As shown in Figure 1, the ADHD RS total score in our unmedicated NT1 sample was significantly higher than that previously reported from mainly medicated children (17.9 (9.5) vs. 12.2 (1.6); $t = 4.612$, $p < 0.0001$) (9). Our subscores were also higher than those reported in a healthy control group (inattentive subscore, 11.0 (6.3) vs. 4.1 (9.274), $p < 0.0001$; hyperactive/impulsivity subscore, 6.9 (4.7) vs. 3.4 (3.4); $t = 5.51$, $p < 0.0001$) (40), but lower than those reported in an ADHD sample (inattentive subscore, 11.0 (6.3) vs. 17.9 (5.5), $t = 8.359$, $p < 0.0001$; hyperactive/impulsivity subscore, 6.9 (4.7) vs. 7.1 (7.1), $t = 5.075$, $p < 0.0001$) (40).

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3.3. ADHD diagnose prior to narcolepsy debut and family history of neurodevelopmental disorders

In two participants (4.0%) an ADHD diagnosis had been given prior to narcolepsy debut, which is consistent with the prevalence of ADHD in the Norwegian population (1.3%, 13, 14). Information regarding family aggregation of neurodevelopmental disorders was available for 40 participants (80 %). In 6 participants (15.0 %) parents reported a

those without (ADHD total score 18.2 (10.3) versus 18.0 (8.7), $p=0.808$; ADHD inattentive score 11.3 (7.4) versus 11.1 (5.4), $p=0.582$; ADHD hyperactive/impulsive score 6.9 (4.8), $p=0.996$).

3.5 Associations between ADHD symptoms and CSF hypocretin-1 level

Comparisons between youths with a level of CSF Hcrt-1 below 40 pg/ml and youths with a level of 40-150 pg/ml revealed no significant differences in the ADHD total score (18.5 (8.4) vs. 16.4 (10.6); $p = 0.410$), inattentive score (11.8 (5.7) vs. 9.0 (5.120), or hyperactive/impulsivity score (6.7 (4.7) vs. 7.05 (5.0); $p = 0.786$).

Within the group of 21 youths with CSF Hcrt-1 level of 40-150 pg/ml there were no significant correlations between CSF Hcrt-1 level and ADHD total score ($\rho = -0.3$), inattentive score ($\rho = -0.23$; $p = 0.312$), or hyperactive/impulsivity score ($\rho = 0.28$; $p = 0.229$).

Please insert table 2 about here

3.6 Associations between ADHD symptoms and sleepiness

The ADHD total and inattentive subscores (but not the hyperactivity/impulsivity subscore) were significantly correlated with parent-reported ESS scores (Table 2). Neither inattentive, nor hyperactivity/impulsivity subscores were correlated with self-reported ESS scores (Table 2). The association between parent-reported ESS and ADHD total score was not significant in univariate or bivariate linear regression analyses (Table 3).

There were no significant associations between ADHD scores and objective daytime sleepiness (mean MSLT SL) with regard to Spearman correlation (Table 2), univariate regression, or multiple linear regression adjusted for age and gender, AHI and PLI (Table 3).

3.7 Associations between ADHD symptoms and sleep fragmentation

There were no significant associations between ADHD total, inattentive or hyperactive/impulsivity scores on the one hand, and sleep stage shift index or awakenings index on the other, either in terms of correlations (Table 2), or in multiple linear regression analyses adjusted for age and gender (step 2, Table 3), or for age, gender, AHI, and awakenings index (step 3, Table 3).

Please insert table 3 about here

4. DISCUSSION

We report for the first time that a sample of unmedicated youths with post-H1N1: of them vaccinated with Pandemrix®) exhibit a high level of ADHD symptoms, especially inattention, but also of hyperactivity/impulsivity. Compared with previous reports, scores in our sample were significantly and considerably higher than in mainly monoamine oxidase deficiency youths (9) and in healthy controls (40), but lower than in youths with narcolepsy (40). Moreover, we found that half of the unmedicated NT1 youths had clinically significant levels of ADHD symptoms, twice as many as previously reported in the predominant

from well characterized European mainly NT1 populations defined by international criteria and using the same ADHD RS. Many drugs that are used to treat narcolepsy are known to reduce ADHD symptoms (i.e. methylphenidate or dexamphetamine). Based on this it is reasonable to postulate that our prevalence estimate of ADHD symptoms in unmedicated NT1 youths is a more unbiased estimator of the true prevalence than those previously reported from mainly medicated pediatric narcolepsy populations. On the other hand, 18.0% of the youths had no ADHD symptoms, implying that ADHD symptoms are not necessarily comorbid or co-existing in NT1. Neither age at inclusion, age of disease onset, age at vaccination, gender nor disease duration were associated with the presence of ADHD symptoms. The prevalence of ADHD diagnoses before narcolepsy onset was comparable to the Norwegian population prevalence estimates (13, 14), and the ADHD scores did not differ between youths with a family history of neurodevelopmental disorder compared to those without. Hence, the high occurrence of ADHD symptoms in our sample was not explained by a high prevalence of pre-existing ADHD diagnosis, or a family history of neurodevelopmental disorder.

The lack of any age or gender influence on ADHD RS scores in our NT1 sample suggests that the ADHD symptoms in our youths do not represent a neurodevelopmental disorder. These disorders are characterized by a higher prevalence in males, and with a decreasing symptom load with age (47).

We did not find an association between CSF Hcrt-1 level and ADHD symptoms, in contrast to previous studies (9, 26, 27). However, others have found associations between

we used to analyze CSF Hcrt-1 in our study has a lower LOQ of 40 pg/ml, and a value below this limit could be of significance in relation to ADHD symptoms. Secondly, the CSF Hcrt-1 levels and the ADHD assessments were not analyzed simultaneously, since the majority of participants (88 % of cases) had a lumbar puncture before inclusion in our study. This implies that some participants may have had a decline in CSF Hcrt-1 level between the time of measurement to the time of the ADHD assessment, as is known to occur in some narcolepsy patients (50, 51). In one study, adult narcolepsy patients with cataplexy experienced a decline with disease duration. However, these narcolepsy patients were atypical in having a normal or intermediate CSF Hcrt-1 level when first measured, in contrast to our typical NT1 sample, in which CSF Hcrt-1 levels were low. Furthermore, no correlation between CSF Hcrt-1 level and disease duration was reported in a sample of pediatric and adult NT1 patients (3). As hypocretin neurons project to, and exert their attention-promoting activity via, brain regions that are directly involved in attention and activity regulation, the ADHD symptoms may be the result of an interaction between low hypocretin output and a relative subclinical dysfunction that existed in these other neurons before the debut of the narcolepsy.

We found a weak but significant correlation between parental reports of sleeping and ADHD symptoms, but no significant association between self-reported sleepiness and ADHD symptoms. Youths with no ADHD symptoms had significantly lower self-reported sleepiness compared with those with ADHD symptoms. Diverging

implying that subjective sleepiness and ADHD symptoms were reported independent of each other. Our findings do not support a theory that the overlap of ADHD symptoms and subjective sleepiness in narcolepsy is caused by a difficulty in teasing out sleepiness from ADHD symptoms (52, 55). Clinically this implies that a narrow focus on ameliorating daytime sleepiness when treating narcolepsy carries the risk of overlooking clinically significant impairments in inattention, impulsivity, and hyperactivity.

To our knowledge, our study is also the first to systematically compare simultaneously assessed ADHD symptoms and subjectively and objectively measured daytime sleepiness in unmedicated youths with narcolepsy. In contrast to the subjective measures of daytime sleepiness, we found no association between ADHD symptoms and the objective sleepiness (MSLT SL). This is in contrast to previous reports of associations between ADHD diagnosis and shorter MSLT SL (18, 55), and also a report of poorer performance on tests of attentional functioning and shorter MSLT SL in unmedicated adult narcolepsy patients (56). These discrepancies towards our findings may be explained by differences in the studied populations (18), inclusion of children with other sleep disorders than narcolepsy (55), and different measures of inattention used (attention test vs. subjective rating scale) since these measures have been reported to have different associations with objective sleep parameters (57). Nevertheless, our results do support previous findings in pediatric and adult narcolepsy studies (27), and are corroborated by the study of Ramm et al, who found no association between performance on the attention test and MSLT SL in a mixed sample of unmedicated adult with central disorders of hypersomnolence (58).

reporters of both ADHD symptoms and sleepiness, and in addition were not blind to narcolepsy status. Another explanation to the subjective-objective discrepancy in the two measures in question, the ESS and the MSLT, assess different aspects of sleep regulation (53) that may be differently associated with ADHD symptoms. While the ESS measures a tendency to fall asleep in various situations, including circumstances where a person would naturally try to stay awake, the MSLT measures a propensity to fall asleep in a given situation (in a dark quiet room). This interpretation is supported by the findings in our sample, correlations between ESS scores and the MSLT SL were weak and non-significant (data not shown), as has been reported in other studies (53). Given that the ESS includes items measuring the ability to stay awake, one could speculate whether the maintenance of wakefulness test (MWT) and the ESS would correlate better than the MSLT. Correlations between MWT and ESS have, however, been reported to be weak to moderate indicating that they measure different aspects of sleepiness the same way as MSLT and ESS (60,61). Future studies on the association between ADHD symptoms and daytime sleepiness should preferably include the MWT in addition to the ESS and the MSLT in order to explore this association offering a more complete description of sleepiness.

Turning to the role of nocturnal sleep fragmentation, ADHD symptoms were not associated with PSG sleep stage shifts, the number of awakenings, and adjusting for AHI and sleep duration did not alter the results. To the best of our knowledge, the association between ADHD symptoms and objective measures of sleep fragmentation has not previously been

different measures of sleep fragmentation from those we used here (sleep efficiency, arousals, wake after sleep onset).

We report a high occurrence of PLM in our population, in accordance with other narcolepsy populations, including children (64). Findings of different periodicity of PLMs in narcolepsy compared to PLMs in restless legs syndrome (RLS) (64) and associations between CSF Hcrt-1 level and PLM index in narcolepsy (65) suggest a different pathophysiology of PLMs in narcolepsy, considered to be more related to a general dysfunctional tonus regulation in NT1 than related to iron deficiency as in PLMs in RLS (65). All the while, as serum or CSF ferritin has not been studied in relation to PLM in narcolepsy (9,64), and ADHD symptoms are associated with iron deficiency (66), the association of iron deficiency for ADHD symptoms in narcolepsy, especially related to PLM, is of interest and should be investigated in future studies.

Rebound effect with increase of especially hyperactive/impulsive symptoms has been described in children with ADHD, (67), as well as increased amount of REM sleep after discontinuation of antiepileptic medication (68). However, the effect of stimulant withdrawal is typically reported the same day as medication discontinuation (67), and rebound effect are typically reported the same day as medication discontinuation (67), hence in our opinion, it is unlikely that withdrawal of stimulant lead to inflated ratings of ADHD symptoms after 14 days off stimulant medication to the extent as to significantly influence our findings.

In our cohort, antiepileptic drugs were additionally tapered off 1-2 weeks prior to the unmedicated period, hence very low levels even prior to the completely unmedicated period.

The relatively small size of our sample means that our findings must be interpreted with caution. However, our results do not suggest that ADHD symptoms in narcolepsy are explained by the core elements of the narcoleptic phenotype, either low CSF Hcr or objectively measured daytime sleepiness, or nocturnal sleep fragmentation. In order to detect significant, but smaller effects of these core elements on ADHD symptoms in narcolepsy, larger or pooled samples would be needed. The lack of association between ADHD symptoms and objective sleep parameters found in our study may also be due to the fact that standard PSG and MSLT measures fail to capture aspects of sleep that could be associated with both narcolepsy and ADHD symptomatology, for instance sleep microstructure deviations such as alterations in cyclically alternating patterns (70, 71) or spindle activity (72, 73). Several cognitive dysfunctions underpin the ADHD behavioral symptoms, which may differ in their relation to hypocretin deficiency or objectively measured sleep characteristics. Various studies, including this one, have featured relatively small samples and may be heterogeneous with respect to underlying cognitive dysfunctions. Still, larger samples including objective measures of cognitive functioning are needed to clarify these matters.

In conclusion, we found that symptoms of inattention, hyperactivity, and impulsivity were more prevalent in unmedicated youths with post-H1N1 NT1, and more so than in previously reported from mainly medicated pediatric narcolepsy patients. Further, the symptoms were not associated with subjective ratings of sleepiness, but not with an ADHD diagnosis |

regarded merely as secondary to sleepiness or sleep fragmentation. Our findings highlight the importance of assessing and treating ADHD symptoms in NT1 separately.

LIMITATIONS

The results of our study must be interpreted in light of its limitations, the most important of which is the lack of a control group. In an attempt to ameliorate some of this drawback we have used norms for the ADHD RS from a culturally, linguistically and socioeconomically similar population (39), and compared our findings with those of a large Spanish population study of ADHD symptom distribution (40). However, several significant variables may vary between these population based groups and our study participants. Participants were not treatment naïve, and measurements of serum ferritin were not available. Also, caution should be used in interpreting our findings as ADHD symptoms were measured by a questionnaire, and not a clinical diagnosis of ADHD. In addition, ADHD diagnosis prior to narcolepsy debut was assessed retrospectively, by combining information from both parental interview and careful review of the patient charts of all participants, and family aggregation of any neurodevelopmental disorder was assessed by parent report and interview by questionnaires and not by direct interview of the individual proband. Further, our study is cross-sectional, so causality cannot be inferred. Finally, we used non-parametric tests to measure correlations, which are robust to undue influence of outliers, but may reduce the ability to detect genuine associations. However, parametric correlation estimates did not produce results that altered the

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