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Psychiatric symptoms in patients with post-H1N1 narcolepsy type 1 in Norway

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Abstract

Study Objectives

Several studies have reported psychiatric comorbidity in patients with narcolepsy type 1 (NC1). The primary aim of this study was to explore the extent of psychiatric symptoms in a cohort of Norwegian NC1 patients, most of whom were H1N1-vaccinated. We also wanted to explore possible causes of the psychiatric symptoms seen in NC1.

Methods

Cross-sectional study. Psychiatric symptoms were assessed by the Achenbach System of Empirically Based Assessment (ASEBA) Child Behavior Check List (CBCL) in children and by Adult Self Report (ASR) in adults.

Results

The mean (*SD*) total T-scores were 58.6 (9.2) for children and 57.0 (9.8) for adults, these being mainly driven by internalizing problems. Internalizing symptom T-scores showed that 37.5% of the children and 33.3% of the adults were in the clinical range of concern. T-scores were lower when the questionnaire's sleep-related items were excluded. However, 27.5% of children and 22.2% of adults still remained within the total psychiatric symptoms clinical range. Psychiatric symptoms and excessive daytime sleepiness were not associated. However, in children fragmented sleep, measured by sleep-stage shift index was significantly negatively associated with all the psychiatric summary scores (all $p \leq 0.020$), and awakening index was negatively associated with externalizing ($p = 0.042$) and total summary scores ($p = 0.042$). In adults, awakening index, but not sleep-stage shift index, was positively associated with internalizing score ($p = 0.015$). Hypocretin-1 levels showed no association with psychiatric symptoms.

Conclusions

We found a high prevalence of psychiatric symptoms in NC1 patients. Fragmented sleep was significantly associated with psychiatric symptoms.

narcolepsy type 1, narcolepsy with cataplexy, psychiatric symptoms, Pandemrix, H1N1

Statement of Significance

Psychiatric symptoms have been reported in patients with narcolepsy type-1 (NC1) in several studies. The reason for the coexistence of psychiatric symptoms and narcolepsy is debated. We found a high prevalence of psychiatric symptoms in NC1 patients and that psychiatric symptoms and symptoms of narcolepsy overlapped. This overlap could, however, only partly explain the high prevalence of psychiatric symptoms in NC1. Interestingly, fragmented sleep was negatively associated with psychiatric symptoms in children, and frequent awakenings were positively associated with psychiatric symptoms in adults, indicating that psychiatric symptoms might be more independently occurring in children with NC1 compared to in adults. Determining the extent of psychiatric symptoms in patients with narcolepsy may improve our understanding and help treatment and facilitate earlier diagnosis.

Introduction

Narcolepsy is a chronic sleep disorder with a global prevalence of 25–50 cases per 100 000 individuals [1–4]. Narcolepsy type 1 (NC1) is caused by the loss of hypothalamic neurons that produce hypocretin, a wakefulness-associated neurotransmitter. The pathophysiological process leading to NC1 is not fully understood, but thought to be due to autoimmunity and a genetic predisposition of the human leucocyte antigen HLA DQB1*06:02. Environmental factors are also likely to play a role [4]. There was an increase in the incidence of NC1 in Norway and several other countries in relation to the H1N1-influenza epidemic of 2009 and the vaccination campaign with Pandemrix [5–7].

The onset of NC1 commonly occurs during adolescence or early adulthood, although the onset of symptoms in childhood is more prevalent than previously assumed [8, 9]. The typical clinical symptoms are (1) excessive daytime sleepiness (EDS), (2) hypnagogic hallucination (HH), (3) sleep paralysis (SP), (4) cataplexy, and (5) nocturnal fragmented sleep [10]. All five main symptoms are not always present simultaneously, and symptoms are commonly misinterpreted as somatic or psychiatric disorders, laziness, or fatigue [11, 12]. The clinical manifestations may vary with age and are often subtle. Children may present with atypical cataplexy or atypical symptoms, such as precocious puberty or hyperactivity and/or irritability. Consequently, the diagnosis of the disease may be substantially delayed [11, 13].

Psychiatric disorders are not only possible differential diagnoses to narcolepsy but often co-exist with narcolepsy. The prevalence of internalizing psychiatric symptoms, such as depression and anxiety, in adults with narcolepsy may be as high as 35% [14–16]. Externalizing psychiatric symptoms, that is, maladaptive behavior towards an individual's environment are not uncommon, and the prevalence of ADHD symptoms is approximately twofold higher in patients with narcolepsy than in the general population [17, 18].

There are several possible reasons for the high prevalence of psychiatric symptoms among patients with narcolepsy. First of all, symptoms of narcolepsy and those of psychiatric disorders overlap, since sleep disturbances are diagnostic criteria for several psychiatric disorders [19]. Second, psychiatric symptoms may arise as a consequence of the disease burden of narcolepsy, or even as a consequence of EDS, which is the most prominent symptom in patients with narcolepsy [20]. Finally, without discounting the plausible explanations above, the hypocretin system might also play a role in the pathogenesis of psychiatric disorders [15, 16, 21], since it projects widely through the brain, affecting several key structures [21, 22].

The primary aim of the present study was to explore the extent and characteristics of psychiatric symptoms among children and young adults who developed NC1 after the H1N1-influenza epidemic and vaccination campaign in 2009 in Norway. We hypothesized a high prevalence of psychiatric symptoms. We also wanted to explore possible causes of the coexistence of narcolepsy and psychiatric symptoms. Is this coexistence due to an overlap between psychiatric symptoms and narcolepsy, or is EDS the most important factor? Also, are hypocretin-1 levels associated with psychiatric symptoms? Determining the extent of psychiatric symptoms in patients with narcolepsy may improve our understanding and thereby help treatment and facilitate earlier diagnosis.

Methods

Study design

This is a cross-sectional study of psychiatric symptoms in NC1 patients, most of whom were H1N1-vaccinated.

Setting and participants

The study was performed at the Norwegian Center of Expertise for Neurodevelopmental Disorders and Hypersomnias (NevSom), Oslo University

Hospital, Ullevål, between March 2015 and September 2017. The study was approved by the Regional Committees for Medical and Health Research Ethics (REK) (REK-number 2014/450).

Inclusion and exclusion criteria

Inclusion criteria were: age, 5–59 years; onset of narcolepsy symptoms after autumn 2009; and NC1 diagnosis based on the International Classification of Sleep Disorders (3rd edition) (ICSD-3) [10]. Participants not fulfilling all the inclusion criteria, or who had another severe medical disorder, were excluded.

Procedure

Participants and their first-degree relatives were hospitalized for 2–4 days. They were educated about narcolepsy and kindergarten/school/work support by a specialized team consisting of a senior doctor specialized in neurology and sleep medicine, a specialist nurse and/or specialist educator, and, in the case of patients younger than 20 years, a child psychiatrist. All participants underwent overnight polysomnography (PSG) followed by a multiple sleep latency test (MSLT) with five nap opportunities at 2-hour intervals. Their circadian rhythm was monitored with actigraphs (Actiwatch Spectrum Plus, Phillips) for 10–14 days prior to the sleep investigations. Sleep stage and associated events were scored according to AASM version 2.2 [23]. The number of sleep-stage shifts and number of awakenings were counted, and the number of these events divided by the total sleep time (sleep-stage shift index and awakening index), were used in the analysis as measures of sleep stability. Blood tests were done to establish HLA type and to control for routine blood parameters. A lumbar puncture to sample cerebrospinal fluid (CSF) was performed at local hospitals, and the level of hypocretin-1 in CSF was measured at the Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, by the previously described method [24]. Hypocretin-1 levels < 150 pg/ml were considered low [25]. Questionnaires were collected in relation to inclusion.

Questionnaires

Psychiatric symptom questionnaires.

To assess psychiatric symptoms, we used the Norwegian version of the Achenbach System of Empirically Based Assessment (ASEBA) Child Behavior Checklist (CBCL) for patients aged 6–18 years, as none of the patients were younger than 6 years of age at the time of inclusion. The corresponding Adult Self Report (ASR) was used for patients aged 18–59 years. ASEBA is a widely used tool for assessing psychiatric symptoms such as adaptive and maladaptive functioning, with comparable scales across age ranges [26, 27]. The CBCL consists of 120 items for scoring patients on eight syndrome scales: anxious/depressed; withdrawn/depressed; somatic complaints; social problems; thought problems; attention problems; rule-breaking behavior; and aggressive behavior. The ASR is equivalent to the CBCL, except that in the ASR the social problem syndrome scale is replaced by that of intrusive behavior. Each item is scored on a three-point response scale, where 0 means “not true”, 1 is “somewhat or sometimes true”, and 2 is “very often true”. A sum score is calculated for each syndrome scale. Five of the syndrome scales for children and six for adults are also used to derive two broad grouping scores: an internalizing score (anxious/depressed, withdrawn/depressed and somatic complaints) and an externalizing score (rule-breaking behavior, aggressive behavior and intrusive behavior [adults only]). The other syndrome scales, three for children and two for adults (thought problems, attention problems and social problems [children only]), are not considered to be components of either the internalizing or externalizing scores, but, in conjunction with the latter, they are used to derive a total score. Higher scores indicate poorer functioning. The standards and norms are the result of empirical findings. For each profile, normalized T-scores are assigned to total scores according to the percentiles for raw scores in a normative sample. The T-scores are based on epidemiological data for children and adults referred for evaluation of behavioral problems. The scores are set to discriminate between normal and clinical levels [28, 29]. The well-validated and reliable instrument provides comparison with test normative data and reduces the need for a control group. A comparison of CBCL results from 1991 and 2007 has shown overall stability in emotional and behavioral problems in the Norwegian population [26, 30]. The raw scores of CBCL and ASR were manually scored by us and converted into T-scores to facilitate comparison. The 50th percentile corresponds to a T-score of 50, and indicates that half of the population is above and half of the population is below this score. For the syndrome scales, the normal range is considered to be a T-score below 65, borderline cases having scores from 65 to 69, and clinical cases having values of 70 or more; patients scoring in the clinical range should be considered to have a problem. For the broad grouping scores (internalizing, externalizing and total scores), the normal range is considered to be a T-score of less than 60, borderline patients having scores between 60 and 63, and values of 64 or more being considered to lie in the clinical range. A T-score of 70 or more, for both syndrome scales and the broad grouping scores, is at the 97th percentile of the normative non-referred population.

Narcolepsy questionnaires.

Subjective core narcolepsy symptoms (cataplexy, EDS, HH, SP) were assessed with the Stanford Sleep Questionnaire (SSQ), including the Epworth Sleepiness Scale (ESS), which gives scores ranging from 0 to 24 [31]. The same version of ESS was used for children and adults. All participants were requested to answer the questions as if they had been in the given situation, if the given situation had not taken place. ESS scores of 10 or more are considered to indicate increased daytime sleepiness [32].

Statistics

Data were analyzed with IBM SPSS version 23. Data are presented as frequencies and means (with *SD* or 95% confidence interval [CI]), as appropriate. Multiple linear regression analyses, adjusted for age and gender, were used to assess the association between scores for psychiatric symptoms and ESS, sleep latency in MSLT, sleep-stage switch index, awakening index and CSF hypocretin-1 concentration (pg/ml). We performed inference on model covariates using Wald tests on 1 *df* from a multiple linear regression model. Values of $p \leq 0.05$ were considered statistically significant.

Results

In December 2014, 91 individuals with onset of narcolepsy after the autumn of 2009 were identified from our national cohort of narcolepsy patients. They were invited to participate in the study and given with the baseline questionnaires. An additional 47 individuals were identified and invited to participate during 2015 and 2016. Thirty eight individuals declined to participate in the study, 15 failed to answer or returned incomplete questionnaires, and 9 individuals were excluded because they did not fulfill all the inclusion criteria. This left a total of 76 participants.

Demographic, clinical and laboratory characteristics of the 76 participants are presented in Table 1. 74/76 patients were Caucasian, one patient was half Caucasian and half Arabic and one patient half Caucasian and half Latin American. 70/76 patients had been H1N1-vaccinated with Pandemrix prior to onset of NC1. With the exception of one case, all patients were HLA DQB1*0602-positive. This child, aged 7 years at inclusion, was hypocretin-deficient and half Caucasian and half Latin American. In addition, he had normal PSG/MSLT, but narcolepsy was confirmed from the patient's low level of hypocretin-1 in CSF.

Table 1.

Demographic, clinical, and laboratory characteristics and medication in children and young adults with narcolepsy type 1

	Children	Adults
	40	36
Female/male	20/20	27/9
Age (year, mean)	13.7 (2.9)	27.8 (11.9)
Pandemrix vaccinated (yes)	36/40	34/36
Hypocretin level in CSF (pg/ml)		
Mean hypocretin-1 levels	56.3 (25.2)	49.8 (26.4)
40–150 (low, but detectable)	17/39	9/33
<40 (undetectable)	17/39	23/33
Low, exact value missing	5/39	1/33
HLA DQB1*06:02		
Positive	38/39	36/36
Symptoms		
Excessive daytime sleepiness	40/40	33/33
Cataplexy	37/40	34/36
Hypnagogic hallucinations	31/40	32/36
Sleep paralysis	23/40	31/36
Mean Epworth sleepiness scale (*SD*)	13.8 (4.4)	15.4 (5.2)
PSG and MSLT (yes*)	39/40	36/36
SOREM (mean)	4.3 (1.1)	4.5 (1.0)
MSLT (minutes, mean)	4.1 (5.3)	2.1 (1.5)
Sleep-stage shift index (PSG) (mean)	13.2 (4.3)	12.1 (3.1)
Medication (yes)		
Methylphenidate	25/40	15/36
Modiodal	14/40	15/36
Venlafaxine	6/40	8/36
Sodium oxybate	11/40	13/36
Fluoxetin	3/40	4/36

CSF, cerebrospinal fluid. Reference range for hypocretin; >200 pg/ml: Normal, <150 pg/ml: Possible narcolepsy, 150–200 pg/ml: Intermediate value. Measurement range of method 40–1280 pg/ml.

*The PSG and MSLT test indicated narcolepsy.

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Psychiatric symptoms measured by ASEBA

To investigate possible discrepancies between NC1 patients vaccinated with Pandemrix and non-vaccinated patients, we performed linear regression

analyses to see if psychiatric symptoms for the internalizing, externalizing or total scores, adjusted for age and gender, differed in vaccinated and non-vaccinated patients. We found no statistically significant differences (data not shown), though the analyses were not well-powered. The two groups were subsequently analyzed together. Even if small, undetected differences between the two groups exist, it is unlikely that this pooling would affect model parameter estimation.

The mean (*SD*) total T-scores were 58.6 (9.2) for children and 57.0 (9.8) for adults, these being mainly driven by internalizing problems. The mean (*SD*) internalizing T-scores were 61.1 (9.1) for children and 60.6 (11.0) for adults, leaving 37.5% and 33.3% in the clinical range for internalizing problems, respectively. For children and adults, the high internalizing scores were mainly driven by the somatic complaint syndrome scale (mean [*SD*] T-score: 65.5 [8.5] and 63.1 [8.9]). We found that 32.5% of the children had T-scores in the clinical range on the thought problem syndrome scale. The T-scores in adults showed that 27.8% were in the clinical range of the attention problem syndrome scale (Table 2).

Table 2.

Psychiatric symptom's T-score and the percentage of patients in borderline and clinical range of concern

	Children (*n* = 40)			Adults (*n* = 36)		
Psychiatric symptoms	Mean (*SD*)	Borderline range%	Clinical range%	Mean (*SD*)	Borderline range%	Clinical range%
Internalizing score	61.1 (9.1)	22.5	37.5	60.6 (11.0)	19.4	33.3
Anxiety/depressed	55.6 (6.8)	7.5	7.5	59.5 (9.8)	8.3	11.1
Withdrawn/depressed	61.7 (8.7)	20.0	22.5	58.3 (6.9)	19.4	5.6
Somatic complaints	65.5 (8.5)	22.5	25.0	63.1 (8.9)	11.1	27.8
Externalizing score	53.1 (9.4)	7.5	15.0	53.2 (9.7)	11.1	11.1
Aggressive behavior	56.4 (7.8)	5.0	10.0	57.6 (6.8)	16.7	2.8
Rule-breaking behavior	54.1 (4.7)	2.5	0	54.2 (5.5)	2.8	2.8
Intrusive behavior				52.6 (5.5)	0	2.8
Thought problems	63.6 (8.9)	12.5	32.5	58.1 (8.1)	2.8	16.7
Attention problems	58.9 (7.9)	17.5	7.5	66.0 (8.1)	25.0	27.8
Social problems	55.6 (7.1)	7.5	7.5			
Total score	58.6 (9.2)	12.5	30.0	57.0 (9.8)	11.1	25.0

Borderline range (BR) for syndrome scale, T-score 65–70; clinical range (CR) for syndrome scale, T-score ≥ 70; BR for broadband scale, T-score 60–63; CR for broadband scale, T-score ≥ 64.

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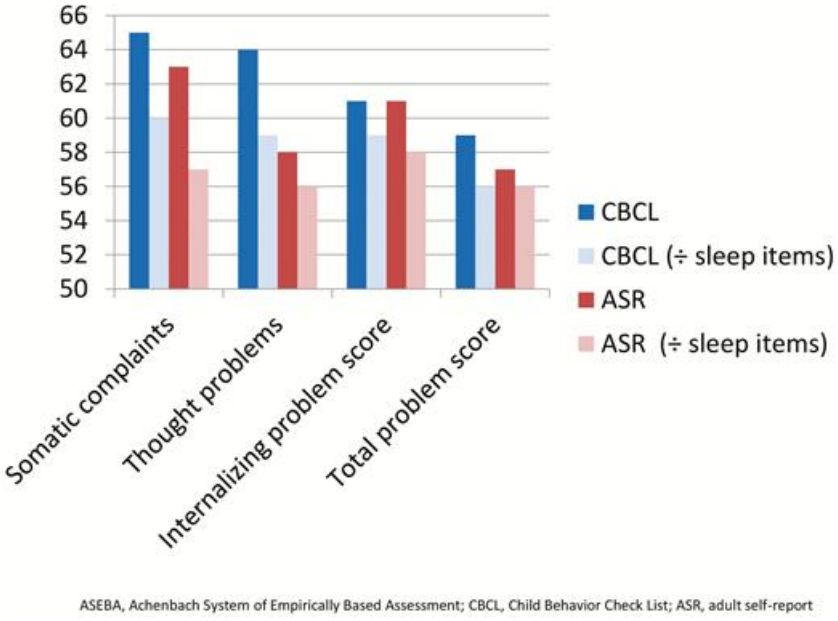
Symptom overlap

Removing the items concerning sleep/core narcolepsy symptoms (six items for children and five items for adults) yielded lower T-scores for all the syndrome scales. Paired-sample *t*-tests revealed statistically significant differences between the questionnaire scores with the sleep items/core narcolepsy symptoms included and excluded (all $p < 0.01$) (data not shown). In children, the mean (95% CI) total T-score for the complete questionnaire (sleep items/core narcolepsy symptoms included) was 58.6 (55.6, 61.5), and 56.5 (53.4, 59.5) when those items were omitted. In adults, the mean (CI) total T-scores were 57.0 (53.7, 60.3) and 55.9 (52.7, 59.0), respectively (Figure 1). After normalizing for the excluded sleep items, we calculated the expected T-scores to be 55.7 in children and 54.6 in adults. Thus, in spite of the decline in T-scores, 27.0% of the children and 22.2% of the adults still presented with total psychiatric symptoms in the clinical range, even when sleep items were excluded from the analyses.

Figure 1.



ASEBA, Achenbach System of Empirically Based Assessment; CBCL, Child Behavior Check List; ASR, adult self-report

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T-scores for psychiatric symptoms measured by ASEBA.

Association between sleep parameters, hypocretin-1 levels, and psychiatric symptoms

The chosen explanatory variables are considered as core NC1 phenomena which could possibly impact psychiatric symptoms. We examined the associations between MSLT, sleep-stage switch index and hypocretin-1 levels, and the outcomes; internalizing, externalizing and total psychiatric symptoms score, adjusted for age and gender. In each model examining MSLT, sleep-stage switch index or levels of hypocretin-1, the remaining two covariates of the group of three were included for further adjustment.

The p-value that follows unless otherwise noted is obtained using Wald tests on 1 df from a multiple linear regression model. We found no significant association between the summary scores of psychiatric symptoms and mean sleep latency (MSLT), adjusted for age and gender (all $p \geq 0.57$) (Table 3). The results were supported by a separate linear regression of the summary scores on ESS, adjusted for age and gender (all $p \geq 0.36$) (data not shown). We found a statistically significant negative association between the sleep-stage shift index and psychiatric symptoms internalizing, externalizing and total score in children ($\beta = -0.9$, $\beta = -1.2$, $\beta = -1.2$, respectively, all $p \leq 0.020$) (Table 3). This means that for a 1-unit increase in sleep-stage shift index, we would expect a −0.9, −1.2, and −1.2 decrease in psychiatric symptoms internalizing, externalizing and total score, respectively, when adjusted for age, gender, MSLT and Hypocretin-1. In a separate linear regression model, awakening index was negatively associated with externalizing and total psychiatric symptoms scores in children ($\beta = -2.4$, $p = 0.042$ and $\beta = -2.3$, $p = 0.042$) and positively associated with psychiatric symptoms internalizing score in adults ($\beta = 4.2$, $p = 0.015$) (data not shown). Neither of the summary scores was associated with the level of hypocretin-1 (all $p \geq 0.12$). Male gender was negatively associated with psychiatric symptoms internalizing score and total score in adults ($\beta = 11.6$, $p = 0.027$ and $\beta = -9.5$, $p = 0.043$), respectively) (Table 3). We found no significant association between disease duration and psychiatric symptom's internalizing, externalizing or total score in neither children or adults in a linear regression model, adjusted for age and gender (data not shown).

Table 3.

Associations between psychiatric symptoms (measured by ASEBA) and mean sleep latency, sleep-stage shift index and hypocretin-1 in patients with Narcolepsy type 1

	Children						Adults			
	Internalizing score		Externalizing score		Total score		Internalizing score		Externalizing score	
	β (95% CI)	*P*-values	β (95% CI)	*P*-values	β (95% CI)	*P*-values	β (95% CI)	*P*-values	β (95% CI)	*P*-values
Age	−0.6 (−2.0, 0.8)	0.38	−0.9 (−2.3, 0.5)	0.21	−1.1 (−2.4, 0.1)	0.08	−0.3 (−0.7, 0.1)	0.10	0.0 (−0.3, 0.4)	0.85
Gender	−2.1 (−10.1, 5.9)	0.59	−4.9 (−12.8, 3.1)	0.22	−6.5 (−13.5, 0.6)	0.07	−11.6 (−21.8, −1.4)	0.027*	−5.8 (−15.0, 3.5)	0.21
Mean sleep latency	−0.2 (−0.9, 0.5)	0.57	0.1 (−0.8, 0.7)	0.88	−0.1 (−0.7, 0.5)	0.75	0.4 (−2.3, 3.2)	0.76	0.1 (−2.4, 2.6)	0.92
Sleep-stage shift index (PSG)	−0.9 (−1.6, −0.1)	0.020*	−1.2 (−1.9, −0.5)	0.002*	−1.2 (−1.8, −0.6)	0.001*	1.1 (−0.2, 2.3)	0.09	0.6 (−0.6, 1.7)	0.33
Hypocretin-1	−0.1 (−0.3, 0.0)	0.12	0.0 (−0.1, 0.2)	0.69	−0.0 (−0.2, 0.1)	0.59	−0.1 (−0.2, 0.1)	0.45	0.0 (−0.1, 0.2)	0.54

Linear regression, *p-value ≤ 0.05.

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Discussion

The main finding from the current study of H1N1-vaccinated NC1 patients was a high prevalence of internalizing psychiatric problems, which is consistent with those of previous studies of patients with sporadic narcolepsy [33, 34]. We found that internalizing problems were mainly driven by the syndrome scale of somatic complaints in children and adults, followed by withdrawn/depressed for children and anxiety/depressed for adults.

Psychiatric symptoms

Somatic complaints are not solely expressed as somatic disorders, but are often seen in patients with psychiatric disorders such as anxiety, depression and somatoform disorders [19]. The prevalence of depressive symptoms in patients with narcolepsy is well documented [11, 14, 20, 35–37], although it is debatable whether it represents a fulminant depressive disorder, or if it is largely a subjective perception. In two controlled studies in adults using formal diagnostic instruments, anxiety and panic attacks, rather than depression, were the most striking findings [16, 38].

Our study also revealed a high prevalence of thought problems. Extreme withdrawal combined with thought problems might be early signs of psychosis and are suitable for psychiatric risk screening [39]. Clinically relevant similarities between NC1 and schizophrenia have been demonstrated [40], but a clear association has not been established. There are even some reports of patients with narcolepsy and schizophrenia [34, 41], although other studies have cast doubt on this association [38, 42]. We found attention problems to be most prominent in adults. Previous studies have shown a high prevalence of Attention Deficit Hyperactivity Disorder (ADHD) in children and in adults [14, 17, 18, 43, 44]. Lecendreux *et al*. found that the severity of ADHD symptoms in children were associated with increased levels of EDS [17]. Accordingly, Lopez *et al*. proposed that ADHD symptoms (mainly with adulthood onset) would be consequences of EDS as they found overlap between EDS, inattention and hyperactivity in patients with central hypersomnia and ADHD [43]. Given our results, it is therefore possible that some of the attention problems seen in our cohort are due to narcolepsy symptoms themselves, and that this is more pronounced in the adult population. The medications used to treat narcolepsy that normally has a beneficial influence on both cognitive and psychiatric symptoms such as attention problems [17] might be attenuated in this population.

Overlap of symptoms

The psychiatric symptoms and the core narcolepsy symptoms overlap to some extent, in particular for the somatic complaints syndrome scale. However, the percentage of patients in the clinical range for the psychiatric symptoms total score remained high, even when sleep items were excluded from the analyses.

Psychiatric symptoms secondary to narcolepsy

Internalizing behavior reflects how well a person adapts to the environment, and the internal distress this may cause [33, 45]. It is therefore plausible that even though there was a decline in psychiatric symptoms after excluding sleep items, the burden of narcolepsy as a chronic disorder may partially explain some of the psychiatric symptoms seen in NC1 patients. This is in line with the study by Rocca *et al*., who noted that children with NC1 were similar to children with epilepsy and migraine with respect to the psychiatric symptom load in terms of somatic complaints and thought and attention problems [34]. Furthermore, studies have shown that patients with obstructive sleep apnea (OSA), asthma and arthritis have more behavior problems, in particular, internalizing problems, compared to healthy controls [46–48]. In other somatic disorders, such as in Ménière's disease, anxiety caused by the burden of chronic exposure to anxiety-inducing situations is common [16, 49]. With respect to the disabling symptoms in narcolepsy, the same explanation might be considered to apply for patients with this disease. It is possible that the psychosocial distress described in patients with narcolepsy as a result of being afraid of falling asleep or of cataplexy-inducing situations may lead to social anxiety, withdrawal, and depression.

Psychiatric symptoms secondary to EDS

Contrary to what has been shown in other studies [20, 50], we observed no association between psychiatric symptoms and EDS measured by ESS and sleep latency in MSLT. One previous study reported a similar psychiatric symptom load when comparing children with narcolepsy and children with EDS without narcolepsy, implying that EDS is the main disadvantage for children with narcolepsy [20]. In line with this, psychiatric symptoms are observed in idiopathic hypersomnia [50] and in healthy children with daytime sleepiness [51]. Furthermore, EDS and fatigue have been associated with ADHD symptoms [17, 52]. Our negative findings might be due to ceiling effects or inherent flaws in the instrument for measuring EDS, though exploration of the marginal distribution of ESS does not indicate that ceiling effects would significantly affect model fit.

Surprisingly, we found a negative association between the sleep-stage shift index and the awakening index and psychiatric symptoms in children. Awakening index was positively associated with psychiatric symptoms internalizing score in adults, which is in line with some studies indicating that behavior problems might be associated with sleep problems such as fragmented sleep [53–55]. In children, subjectively reported sleep fragmentation is not that uncommon [56], and one might speculate that children with narcolepsy might adapt better than adults. However, this cannot explain the negative association between sleep fragmentation and psychiatric symptoms in children. Furthermore, it is possible that parents of children with high levels of sleep fragmentation will focus more on symptoms related to sleep deprivation and less on psychiatric symptoms while parents of children that have a more normal sleep do the opposite. Lewin *et al*. reported that children with mild and severe OSA had more behavior problems than controls. Interestingly children with mild OSA had more behavior and emotional problems than children with severe OSA [46].

Psychiatric symptoms and hypocretin

We found no association between psychiatric symptoms and hypocretin-1 levels in CSF. Hypocretinergic neurons project and interact with several areas of the brain involved in emotion, cognition, reward and stress reactions [21, 22, 57]. It is therefore plausible that the greater prevalence of psychiatric symptoms seen in patients with narcolepsy may reflect a common pathology involving the hypocretin system, rather than a distinct comorbidity. This is disputed, as some studies have shown significantly lower hypocretin-1 levels in CSF in patients with psychiatric disorders, such as major depression, while others have not found such an association [17, 58–60].

Narcolepsy and psychiatric disorders are both associated with certain genetic predispositions [61, 62], so a common genetic vulnerability or biological pathways other than those of the hypocretin system may be involved.

Limitations

There are some limitations to our study. First, it is a cross-sectional study, so that model parameter of interest may not have a causal interpretation despite covariate adjustment. Second, the study lacks a control group, though the use of well-validated and reliable measures with nontrivial variation in regressor variables allows for uncompromised and generalizable model estimation. Furthermore, we used parent reports for patients younger than

18 years and self-report for those over 18 years of age. We acknowledge that this is potentially a limitation. However, due to the age span of our cohort, the use of either a self-reported version or a parent-reported version alone would have produced its own bias. We also acknowledge that our results would have been more compelling if all patients were evaluated by a trained psychiatrist using diagnostic tools. Finally, the use of Epworth Sleepiness Scale for Children and Adolescents, (ESS-CHAD) would have increased the validity of our results.

Conclusion

We found a high prevalence of psychiatric symptoms in H1N1-vaccinated NC1 patients in Norway, which were mostly driven by internalizing problems. This is only partly explained by the overlap between psychiatric and narcolepsy symptoms. We found no association between psychiatric symptoms and subjective EDS or mean sleep latency in MSLT. However, sleep-stage shift index and awakening index were negatively associated with psychiatric symptoms in children and awakening index was positively associated with internalizing symptoms in adults. Psychiatric symptoms were not associated with hypocretin-1 levels.

Our findings highlight the importance of thoroughly examining the psychiatric symptoms seen in patients with narcolepsy in order to enable proper medical and psychological treatment. Further studies exploring the coexistence of psychiatric symptoms and narcolepsy are warranted.

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Conflict of interest statement. None declared.

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