https://doi.org/10.5664/jcsm.9052

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Single center analysis of patients with H1N1 vaccine-related narcolepsy and sporadic narcolepsy presenting over the same time period

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Study Objectives: We aimed to describe the clinical features of narcolepsy in patients referred to our sleep center between 2009 and 2016, and to compare these features across age groups and between sporadic vs AS03-adjuvanted H1N1 influenza vaccine-related patients.

Methods: This is a retrospective, consecutive study of adult and pediatric narcolepsy patients in the Republic of Ireland. All participants underwent structured assessments, including polysomnography and the Multiple Sleep Latency Test. Brain magnetic resonance imaging, hypocretin levels, and human leukocyte antigen typing were also carried out on the majority of patients. Patients were compared across age groups as well as etiology.

Results: The conditions of 40 (74%) patients were vaccine-related. The median age was 13.5 years and time from symptom onset to diagnosis was 112 weeks. Median time from vaccination to symptom onset was 26 weeks. In children, hypnogogic hallucinations and sleep paralysis were less frequent than in adults (17% vs 67%, $P = .018$ and 0% vs 75%, $P < .0005$). Sleep latency determined by the Multiple Sleep Latency Test was shorter in children than adults (median 1.75 vs 4 minutes, $P = .011$). Patients with vaccine-related and sporadic narcolepsies had typical clinical presentations. Vaccine-related patients had longer polysomnography latency (median 10.5 vs 5 minutes, $P = .043$), longer stage N2 sleep (209.6 ± 44.6 vs 182.3 ± 34.2 minutes, $P = .042$), and a trend toward longer total sleep times ($P = .09$). No differences were noted in relation to Multiple Sleep Latency Test, hypocretin, human leukocyte antigen typing, and magnetic resonance imaging.

Conclusions: Results show that vaccine-related patients greatly outnumbered sporadic patients during the study period and suggest that sporadic and vaccine-related narcolepsy are clinically similar entities.

Keywords: narcolepsy, influenza A, subtype H1N1, AS03-adjuvant, Pandemrix, influenza vaccine, hypocretin-1, HLA-DQB1*0602.

Citation: Ferguson D, Wrigley S, Purcell E, et al. Single center analysis of patients with H1N1 vaccine-related narcolepsy and sporadic narcolepsy presenting over the same time period. *J Clin Sleep Med*. 2021;17(5):885–895.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Vaccination with AS03-adjuvanted H1N1 influenza vaccine was associated with an increased incidence of narcolepsy in several jurisdictions, especially in children. Our center, serving the entire population of the Republic of Ireland, also noted an increase in cases, and this study was designed to compare sporadic and vaccine-related patients presenting contemporaneously.

Study Impact: The results indicate that sporadic and vaccine-related narcolepsies are very similar in terms of symptoms, signs, and diagnostic findings. We are of the opinion that both diagnoses share the same underlying pathophysiological mechanisms albeit triggered in different manners.

INTRODUCTION

Narcolepsy is a sleep disorder classically characterized by the clinical tetrad of excessive daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis. The presence of cataplexy as well as ancillary investigations distinguish narcolepsy type 1 (NT1) from narcolepsy type 2 (NT2).[1] Narcolepsy is predominantly a sporadic disorder but familial and secondary causes are also recognized. Other clinical features may include sleep disturbance and parasomnias, neuropsychiatric issues, metabolic abnormalities, and autonomic dysfunction.[2]

Narcolepsy is known to be caused by loss of hypocretin-secreting neurons in the lateral hypothalamus, leading to hypocretin-1 (orexin A) deficiency.[3,4] Detection of low hypocretin-1 levels in cerebrospinal fluid is used in clinical practice to support a diagnosis of narcolepsy.[1] The exact mechanism behind this loss of hypocretin-releasing neurons remains unknown. It has long been recognized that human leukocyte antigen (HLA) class II genetics plays a role in sporadic narcolepsy.[5] In fact, in a multinational European study, 98% of patients with NT1 were found to carry HLA-DQB1*0602, while 18% to 30% of the general European population carry it.[2,6,7] On the other hand, HLA-DQB1*0602 is present in 75% of patients with familial narcolepsy and in 40% to 60% of those with narcolepsy type 2 and idiopathic hypersomnia.[2,8–10] Furthermore, in monozygotic twins who were homozygous for HLA-DQB1*0602, 1 twin had a diagnosis of narcolepsy type 1, while the other was unaffected.[11] Therefore, one's HLA genetic makeup is not sufficient to explain narcolepsy; it is considered to be a combination of an

underlying genetic predisposition and a triggering environmental stimulus, giving rise to a probable autoimmune destruction of neurons in the lateral hypothalamus.

Further evidence for environmental triggers came following the observation of an increased incidence of narcolepsy after the influenza A H1N1 vaccination program during the winter of 2009–2010; in particular, the anti-streptolysin O (ASO)3-adjuvanted vaccine was considered as a trigger.[12–16] This observation was reproduced in several European countries, including Ireland, where the ASO3-adjuvanted vaccine was used.[17–19] At the same time, however, an increased incidence of narcolepsy was reported in China, where the vaccine had not been used, therefore suggesting that the H1N1 subtype of the influenza A virus, by itself, could also act as an environmental trigger.[20]

When the initial reports of narcolepsy in association with ASO3-adjuvanted H1N1 vaccine were published, there was a suggestion that vaccine-related patients demonstrated more abrupt onset and a shorter duration of illness prior to diagnosis, implying a more severe phenotype.[14,17,21] Another difference was the predilection for children.[14,16] In Sweden and Finland, 100% of patients with vaccine-related narcolepsy were confirmed carriers of the HLA-DBQ1*0602 allele.[14,16]

To date it is still unclear whether ASO3-adjuvanted H1N1 vaccine–related narcolepsy represents a distinct subtype of narcolepsy with an underlying neurobiology different from sporadic narcolepsy, or whether they share the same pathophysiology. This study was conducted with the aim of defining in detail the clinical characteristics of patients with narcolepsy across different ages, all of whom were diagnosed in a single center between 2009 and 2016, and to assess whether there are any differences in the clinical features of vaccine-related narcolepsy that could imply an underlying pathobiology different from sporadic narcolepsy.

METHODS

Participants and testing

This was a retrospective, consecutive study looking at the clinical and polysomnographic findings of patients referred to the Sleep Disorders Clinic in The Mater Private Hospital, Dublin, between January 2009 and May 2016. This clinic was the only tertiary referral center in the Republic of Ireland for pediatric and adult narcolepsy at the time and served a population of over 4.7 million.

Originally, 94 patients diagnosed with narcolepsy during the specified time period were approached to participate. Fifty-three responded positively. In addition, 2 pediatric patients seen earlier were invited to join the study and 1 accepted. Written informed consent was received from all patients/legal guardians. The study was approved by the joint Mater Misericordiae University Hospital/Mater Private Hospital ethics committee. The majority of patients were referred to the Sleep Disorders Clinic by the department of pediatric neurology in Temple Street Children's University Hospital, Dublin.

All patients were assessed at their first visit by both principle investigators, CC and EP, using a standardized clinical evaluation; this included basic demographic information [age, sex, body mass index (BMI)], narcolepsy-specific clinical information (presence of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and other sleep disorder-related symptoms), and an assessment of symptom severity (frequency of naps and cataplectic episodes). Patients with narcolepsy were considered vaccine-associated if onset of symptoms occurred within 24 months of ASO3-adjuvanted H1N1 pandemic influenza vaccination (Pandemrix).

All participants underwent overnight polysomnography (PSG) and the Multiple Sleep Latency Test (MSLT) in the single specialized sleep laboratory in the Mater Private Hospital. The older studies were carried out on Sleep Lab Pro hardware (VIASYS Healthcare GmbH, Hoechberg, Germany) with Somnostar software (CareFusion Ltd., Hampshire, United Kingdom). Later studies were recorded on SOMNOscreen plus hardware with Domino software (SOMNO*medics* GmbH, Randersacker, Germany). Recorded information included electroencephalography (C4-M1, C3-O2), electro-oculography (left and right), electromyography (EMG; submental, right and left tibialis anterior), respiratory variables [nasal cannula, oral thermistor, thoracic and abdominal effort, peripheral capillary oxygen saturation (SpO_2)], electrocardiogram, and body position. A subset of 15 randomly chosen patients who had been studied on the VIASYS system received an analysis of their EMG tone during the last rapid eye movement (REM) cycle performed (phasic and tonic events in masseter and tibialis anterior muscles per hour of REM sleep). Masseter was chosen as it was the most reliable electrode. The last cycle of REM was chosen for analysis as it is, in the senior author's experience, the longest REM cycle and the richest for data. Scoring was carried out according to the relevant American Academy of Sleep Medicine guidelines of the time. In most patients only 4 naps were recorded on MSLT as the tests were highly abnormal and a fifth nap was not deemed necessary. A proportion of patients underwent cerebrospinal fluid sampling for hypocretin-1 levels (Phoenix Pharmaceuticals assay, Pathology Laboratory, Oxford University Hospitals, England), and serum sampling for HLA DBQ1*0602 status.

Data was collected retrospectively by authors CC and BMcG (EMG), and analyzed by author DF. The manuscript was prepared by DF, SW, and CC.

Statistical analysis

Data was analyzed with SPSS version 25.0 for Macintosh (SPSS Inc., Chicago, IL). Categorical data is presented as an absolute number (n) and percentage (%). Continuous variable normality was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests as well as visual inspection of Q-Q plots. Normally distributed variables are presented as mean values (± standard deviation); nonnormal variables are presented as median values (interquartile range). For normally distributed continuous variables, differences across groups were tested with either independent samples *t* tests or one-way analysis of variance with Tukey's post-hoc pairwise comparisons. For nonnormal continuous variables, differences across groups were tested with either Mann-Whitney *U* tests or Kruskal-Wallis H tests with pairwise comparisons carried out using Dunn's procedure with a Bonferroni correction for

multiple comparisons. Chi-square or Fisher exact tests of independence, with *z*-test column comparisons, were performed to examine the relationships between categorical variables. All significance levels were set at alpha < .05.

RESULTS

Whole group

Data from 54 individuals were analyzed. Half of the cohort was female, 89% were Irish, 5.5% Black-African, and 5.5% White-European. The age at first assessment ranged from 6 to 49 years (median 13.5). Age breakdown is outlined in **Figure 1**. Onset of symptoms was related to ASO3-adjuvanted H1N1 pandemic influenza vaccination in 40 patients (74%). Of the patients with sporadic narcolepsy, 6 had vaccination after symptom onset, 7 had never been vaccinated, and 1 had onset 3 years post-vaccination. The median diagnostic delay for the entire cohort was 112 weeks. Thirty-five (83%) of those who did not consent to the study had vaccine-related and 7 (17%) sporadic narcolepsy.

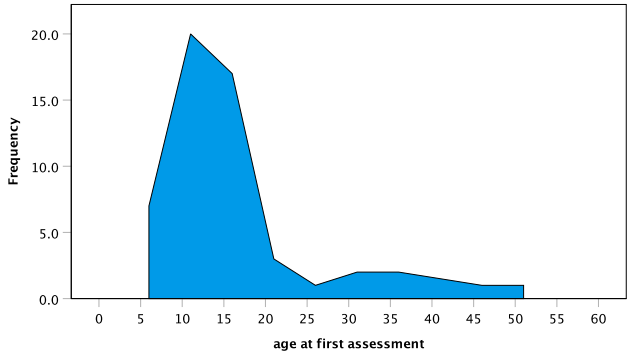
The frequencies of the core narcolepsy and other related symptoms are presented in **Table 1**. Cataplexy, the most frequent ancillary feature, was seen in 87% of patients at initial assessment. The majority (78%) of patients were napping 2 or more times per day. Possibly relevant premorbid conditions were reported in 24 (44%) patients. These included 7 who had already undergone tonsillectomy, 7 with a complaint of upper respiratory tract infections/sore throats, 3 with psychosocial stressors, 2 with minor head trauma, and 5 miscellaneous issues.

All patients had PSG and MSLT (**Table 2**). A smaller proportion (44%) underwent lumbar puncture. Hypocretin levels were abnormal in all patients. Twenty-one patients had a hypocretin level < 50 pg/mL, and 3 patients had a level < 110 pg/mL. Most patients underwent neuroimaging (85%) and HLA subtyping (76%). Abnormalities on neuroimaging are listed in **Table 2**. Ninety-five percent of those tested were HLA DQB1 06*02-positive. Two patients were HLA DQB1 06*02-negative; one had vaccine-related narcolepsy with cataplexy, the second had vaccine-related narcolepsy without cataplexy. Neither had hypocretin measured.

Differences between sporadic and vaccine-related narcolepsy

From a clinical perspective, considering the list of demographic details and symptoms, the vaccine-related and sporadic groups are very similar (**Table 1**). In particular, the groups were evenly matched with respect to age, sex, and BMI. In patients with vaccine-related narcolepsy, symptom onset was noted at a median of 26 weeks post-vaccination and diagnosed at a median of 108 weeks from symptom onset. The diagnostic delay for sporadic narcolepsy was 121 weeks (nonsignificant difference). There were no differences in core narcolepsy features. More vaccine-related patients (65% vs 18%) were found to have irritability upon waking from a nap; χ^2 (1, n = 42) = 5.254, P = .022. Patients with sporadic narcolepsy trended toward being more frequently upset by their cataplexy events; (54% vs 22%) χ^2 (1, n = 45) = 3.043, P = .072. To assess the severity of the condition, the number of classic symptoms at presentation was analyzed and no significant difference was seen between the 2 groups.

Figure 1—Age distribution of the narcolepsy cohort.



Regarding investigation results, both groups were, again, broadly similar (**Table 2**). PSG sleep latency was shorter in the sporadic group; 5 vs 10.5 minutes, U = 382, z = 2.026, P = .043. PSG nocturnal sleep onset rapid eye movement periods (SOREMPs) were seen in 21% of patients with sporadic narcolepsy and 43% of those with vaccine-related narcolepsy, χ^2 (1, n = 54) = 1.174, P = .279. More stage N2 sleep (measured in minutes but not percentage of overall sleep) was seen in vaccine-related patients; 209.6 vs 182.3 minutes, t(52) = −2.081, P = .042. No differences were found in MSLT variables. The median heart rate variability (delta R-R) trended toward being lower in vaccine-related patients compared with sporadic patients; U = 160, z = −1.792, P = .073. No other differences were found between groups.

In the subset with EMG analysis performed, the tone in the last cycle of REM sleep appeared to be elevated in many patients, expressing itself frequently as increases in phasic activity and, to a lesser extent, increases in tonic activity or both simultaneously. Increased phasic EMG tone was seen more frequently on leg EMG than on masseter EMG (P = .00004) and was more in keeping with a persistence of period limb movements of sleep in REM sleep. The increased tonic EMG tone was similar across all EMG electrodes. There was a trend toward more phasic tibialis anterior activity in the sporadic onset group compared to the vaccine-related onset group, t(13) = 2.013, P = .065.

Differences across age groups

Patients were divided into 3 age groups [children (≤ 12 years), adolescents (13–17 years), and adults (≥ 18 years)] for discovery of differences in clinical and paraclinical variables across age groups (**Table 3** and **Table 4**). The frequency of vaccine-related patients, sex, and BMI were similar across groups. Adults were more likely to present with the tetrad of symptoms compared to children (60% vs 0%), and children were more likely to present with just 2 of the 4 core symptoms (78% vs 17%); χ^2 (6, n = 54) = 17.54, P = .002. Adults reported hypnogogic hallucinations more frequently than children [67% vs 17%; χ^2 (2, n = 54) = 7.906, P = .018]. Adults and teenagers reported sleep

Table 1—Demographic and sleep disorder features of the entire narcolepsy cohort, with a comparison of vaccine-related and sporadic patients.

	Whole Group (n = 54)	Vaccine-Related Onset (n = 40)	Sporadic Onset (n = 14)	Diff Between Groups *P*
Demographics/anthropometrics n = 54				
†Age, years	13.5 (6)	14 (6)	13 (11)	.890
Body mass index (*Z*-score)	1.37 (1.05)	1.41 (1.17)	1.26 (0.62)	.552
Female, n (%)	27 (50)	22 (55)	5 (36)	.203
Narcolepsy features n = 54				
Excessive daytime sleepiness (yes), n (%)	54 (100)	40 (100)	14 (100)	1.000
Cataplexy (yes), n (%)	47 (87)	33 (83)	14 (100)	.171
Hypnogogic hallucinations (yes), n (%)	22 (41)	17 (43)	5 (36)	.898
Sleep paralysis (yes), n (%)	18 (33)	14 (35)	4 (29)	.751
How many of the core 4 symptoms were present?				
1	3 (6)	3 (8)	0 (0)	.878
2	27 (50)	19 (48)	8 (57)	
3	12 (22)	9 (23)	3 (21)	
4	12 (22)	9 (23)	3 (21)	
†Time-lag postvaccine to symptom onset (weeks)	—	26 (45)	—	—
†Diagnostic delay (weeks)	112 (90)	108 (82)	121 (355)	.299
Possible prior risk factor (other than vaccination)	24 (44)	15 (38)	9 (64)	.155
Sleep disorder symptoms n = 54, unless otherwise stated				
Daytime napping (n = 52)	51 (98)	38 (100)	13 (93)	.269
≤ 1 naps per day	12 (22)	7 (18)	5 (36)	.362
2 naps per day	20 (37)	16 (40)	4 (29)	.362
≥ 3 naps per day	22 (41)	17 (43)	5 (36)	.362
Zoning out/reduced attention	49 (91)	36 (90)	13 (93)	1.000
Reduced work/school performance	32 (59)	25 (63)	7 (50)	.615
Vivid dreams (n = 53)	45 (85)	33 (83)	12 (92)	.662
Nightmares (n = 53)	28 (53)	23 (58)	5 (39)	.382
Excessive nocturnal waking	42 (78)	31 (78)	11 (79)	1.000
Excessive irritability after napping (n = 42)	22 (52)	20 (65)	2 (18)	.022
Increased weight (n = 52)	23 (44)	15(39)	8 (62)	.259
Reduction in physical activity (n = 53)	21 (40)	18 (45)	3 (23)	.281
Sleep talking	28 (52)	23 (58)	5 (36)	.274
Sleep shouting (n = 53)	10 (19)	10 (25)	0 (0)	.096
Cataplexy features n = 45, unless otherwise stated				
Laughter induced	41 (91)	30 (94)	11 (85)	.567
Neck weakness	34 (76)	25 (78)	9 (69)	.704
Facial muscle weakness	32 (71)	24 (75)	8 (62)	.473
Tongue protrusion	9 (20)	7 (22)	2 (15)	1.000
Falls	13 (29)	10 (31)	3 (23)	.725
Emotionally upset after cataplexy	14 (31)	7 (22)	7 (54)	.072
Lolling (n = 52)	14 (27)	11 (29)	3 (21)	.732
Cataplexy frequency (n = 44)				.205
< 1 per day	16 (36)	10 (32)	6 (46)	—
1–2 per day	19 (43)	16 (52)	3 (23)	—
> 2/variable	9 (20)	5 (16)	4 (31)	—

Data presented as mean (standard deviation), †median (interquartile range), and frequency (%) as appropriate.

Table 2—Investigation results for the entire narcolepsy cohort, with a comparison of vaccine-related and sporadic patients.

	Whole Group (n = 54)	Vaccine-Related Onset (n = 40)	Sporadic Onset (n = 14)	Diff Between Groups *P*
Ancillary investigation results				
HLA typing (n = 41), DQB1 06*02 positive	39 (95)	32 (94)	7 (100)	1.000
Hypocretin testing (n = 24)				
< 50 pg/L	21 (88)	18 (86)	3 (100)	1.000
50–110 pg/L	3 (12)	3 (14)	0 (0)	
Neuroimaging (n = 46), abnormal*	8 (17)	5 (14)	3 (25)	.394
PSG/MSLT results n = 54, unless otherwise stated				
†PSG sleep latency (min)	8.5 (14.3)	10.5 (13.8)	5 (11.5)	.043
†PSG REM latency (min)	67 (94.3)	57.5 (106.3)	70.5 (53.5)	.767
PSG nSOREMP (yes)	20 (37)	17 (43)	3 (21)	.279
†MSLT mean latency (min)	2 (2.1)	2 (2.4)	2 (2.6)	.873
†MSLT number of SOREMPs	4 (1)	4 (1)	4 (1)	.618
†AHI	2 (3)	2 (2)	2 (4)	.351
†Periodic leg movements of sleep (PLMS) index	7 (8)	7 (7)	7.5 (11)	.586
Leg jerks index (n = 53)	15.7 (8.0)	15.2 (8.3)	17.1 (7.4)	.432
†Stage N1 sleep (min)	78.5 (30.9)	68.5(30.7)	77 (35)	.615
†Stage N1 sleep %	16 (7)	16 (7)	17.5 (9)	.488
Stage N2 sleep (min)	202.5 (43.6)	209.6 (44.6)	182.3 (34.2)	.042
Stage N2 sleep %	44 (6)	44.4 (6.1)	41.6 (6)	.139
Stage N3 sleep (min)	96.4 (30.1)	98.0 (29.2)	91.7 (33.2)	.506
Stage N3 sleep %	21 (6)	21 (5.5)	20.8 (7.4)	.973
REM sleep (min)	85.5 (30.5)	85.7 (29.6)	84.9 (33.9)	.936
REM sleep %	18 (6)	19 (6)	19.3 (7.1)	.549
Total sleep time (min)	462.3 (59.1)	470.4 (61.3)	439.4 (47.3)	.092
†Number of REM sleep periods (n = 48)	5 (1)	5 (2)	4.5 (1)	.925
†Wake after sleep onset (min) (n = 53)	47 (52)	43 (55)	62 (51)	.397
†% Sleep efficiency	90 (9)	91 (9)	89 (10)	.281
†Awake index (n = 48)	3.75 (2.5)	3.5 (2.5)	3.75 (3)	.837
Arousal index (n = 49)	17.8 (6.7)	17.0 (9.0)	15.0 (10.8)	.689
†Heart rate (n = 48)	71 (14)	70.5 (11)	75 (23)	.874
†Delta *R*-R (n = 48)	0.6 (0.4)	0.55 (0.3)	0.7 (0.4)	.073
EMG findings during the last REM sleep cycle (n = 15)				
†Submental EMG phasic activity (indices/h)	21 (21.5)	21 (24.3)	11.5 (32.4)	.864
Tibialis anterior EMG phasic activity (indices/h)	54.2 (20.0)	46.5 (18.5)	65.8 (17.6)	.065
†Submental EMG tonic activity (indices/h)	6.5 (13.5)	6.5 (13.8)	4.5 (7.5)	.955
†Tibialis anterior EMG tonic activity (indices/h)	6.5 (10)	2.5 (9.0)	8.3 (11.4)	.328

Data presented as mean (standard deviation), †median (interquartile range), and frequency (%) as appropriate. *Abnormalities included cortical dysplasia (n = 1), pineal gland cyst (n = 1), cerebellar cyst (n = 1), microangiopathic changes (n = 1), pituitary enlargement (n = 1), large arachnoid cyst with mass effect (n = 1), low lying cerebellar tonsils (n = 1), and subcortical hyperintensity (n = 1). AHI = apnea-hypopnea index, Delta *R*-R = median heart rate variability, EMG = electromyography, HLA = human leukocyte antigen, MSLT = Multiple Sleep Latency Test, nSOREMPs = nocturnal sleep onset rapid eye movement periods, pg/L = picogram per liter, PSG = polysomnography, REM = rapid eye movement.

paralysis more frequently than children [75% and 38% vs 0%; $\chi^2(2, n = 54) = 20.223$, $P < .0005$]. Children displayed tongue lolling more frequently than adults [50% vs 0%; $\chi^2(2, n = 52) = 9.075$, $P = .007$]. Children and teenagers were more likely to be irritable after a nap than adults [67% and 60% vs 0%; $\chi^2(2, n = 42) = 9.617$, $P = .007$].

The median PSG sleep latency was different across groups ($\chi^2(2) = 8.346$, $P = .015$), with adults having a significantly longer sleep latency compared to teenagers (21 vs 7 minutes; Bonferroni-adjusted $P = .015$). The median MSLT latency was also different across groups, $\chi^2(2) = 9.037$, $P = .011$. MSLT latency increased from children (1.75 minutes) to adolescents

(2 minutes) to adults (4 minutes). Post-hoc analysis revealed the difference between children and adults was significant (Bonferroni-adjusted $P = .008$). As expected, stage N3 sleep (measured in minutes) was different across groups [$F(2, 51) = 15.394$, $P < .0005$]. It decreased from children (117.6 ± 28.5 minutes), to adolescents (94.9 ± 20.2 minutes), to adults (67.6 ± 24.8 minutes). Tukey post-hoc analysis revealed that the decrease in N3 minutes from children to adolescents [−22.6 minutes, 95% CI (−40.9 to −4.4 minutes)] was significant ($P = .011$), as was the decrease from children to adults [−50.0 minutes, 95% CI (−71.77 to −28.17 minutes), $P < .0005$], and the decrease from adolescents to adults [−27.3 minutes, 95% CI (−48.0 to −6.6 minutes), $P = .007$]. Similarly, percentage of N3 was different across groups, as expected [$F(2, 51) = 10.627$, $P < .0005$]. It decreased from children (24% ± 6%), to adolescents (21% ± 4%), to adults (15% ± 6%). Tukey post-hoc analysis revealed that the decrease in percentage of N3 from children to adults [−8.7, 95% CI (−13.4 to −4.1)] was significant ($P < .0005$), as was the decrease from adolescents to adults [−6.0, 95% CI (−10.3 to −1.6), $P = .005$]. There was no difference in the frequency of nocturnal SOREMPs across age groups ($P = .713$).

Mean heart rate was different across groups [$F(2, 45) = 7.003$, $P = .002$]. As expected, heart rate decreased from children (81 ± 15), to adolescents (71 ± 9), to adults (66 ± 8). Tukey post-hoc analysis revealed that the decrease in heart rate from children to adults [−15.0, 95% CI (−25.3 to −4.7)] was significant ($P = .003$), as was the decrease from children to adolescents [−10.5, 95% CI (−19.6 to −1.3), $P = .021$].

Adults were less likely than children and teenagers to be HLA DQB1 06*02 positive (60% vs 100% in both groups); χ^2 [2, n = 41] = 7.653, $P = .018$.

Sex differences

Apart from a trend toward longer mean-total sleep time for female patients (476 ± 62 vs 431 ± 100 minutes; $t(52) = 1.982$, $P = .053$), no other differences were found between males and females.

Early-onset vs late-onset vaccine-related narcolepsy differences

Vaccine-related patients (n = 40) were dichotomized into 2 groups based on the median time to symptom onset after vaccination. Early presenters (≤ 26 weeks from time of vaccination to symptom onset) and late presenters (> 26 weeks) were compared. There were no differences between groups with respect to clinical or paraclinical variables.

DISCUSSION

This is the second study comparing contemporaneous patients with sporadic and vaccine-related narcolepsy across the age spectrum. It is the first single-center study of an entire nation. It adds to the growing body of knowledge about the clinical features of influenza A (H1N1) vaccine–related narcolepsy and provides evidence to suggest that the phenotypes of vaccine-related and sporadic narcolepsy have only minor differences.

In 2011, the Irish Medicines Board received reports of the onset of narcolepsy following vaccination against influenza A (H1N1) pdmo9 with Pandemrix. A national steering committee was convened to examine the association and their report was published in 2014.[18] A relative risk of 13.9 and absolute attributable risk of 5.3 patients per 100,000 vaccinated children and adolescents was found. This was similar to findings in Finland and Sweden but slightly less than those in Norway and the United Kingdom.[14,16,19,21–23] In Ireland, 339,312 children between the age of 5 and 19 were vaccinated during the winter of 2009/2010, almost 40% of that population.

The cohort described in this paper includes patients dating from January 2009, just prior to the commencement of the influenza H1N1 vaccination program in Ireland. In our experience, one of the major observations over the 8-year period covered by this study was a dramatic increase in young presentations. Prior to 2010 we had seen only 3 children under 13 years in our clinic.

It has long been established that the peak incidence of narcolepsy is in the second decade.[24] Other studies that included a large proportion of vaccine-related patients have reported a young age of presentation, as does ours.[25] Despite the widespread inoculation with Pandemrix of the pediatric population in Ireland, there was no difference in age between our patients with sporadic and vaccine-related narcolepsy. We believe that puberty is a risk factor for the onset of narcolepsy in genetically primed individuals—this may be due in part to immune-mediated factors. The hypothalamus is implicated in pubertal onset,[26] and changes in blood flow or permeability of the blood brain barrier during this time period may play a role in the pathophysiology of narcolepsy.

An increased incidence of childhood narcolepsy since 2009 has been noted elsewhere.[27] This includes populations that did not receive the influenza H1N1 vaccine.[20,28,29] Alternative environmental factors such as influenza H1N1 itself and other upper airways pathogens have been proposed as potential triggers.[20,30] Another important factor at play is the increased public awareness of narcolepsy. It is possible that childhood narcolepsy was widely under- or misdiagnosed and that the publicity surrounding vaccine-related narcolepsy brought it to the fore. It has been reported that there is typically a diagnostic delay of 14 years for narcolepsy.[31] A remarkable finding in our study is that the time lag from onset of symptoms to assessment at a sleep clinic was quite short for all patients. This would favor the argument that the increased incidence of childhood narcolepsy is, in part, linked to greater public awareness of the condition.[28]

Narcolepsy features in different age groups

The classic narcolepsy tetrad was described in 1957 by Yoss[32] and is widely quoted; however, 78% of our children had only 2 of these classic symptoms. Sleep disturbance, nightmares, and sleep talking/shouting were more commonly seen in children than hypnogogic hallucinations or sleep paralysis. It is important for practitioners not to dismiss a possible narcolepsy diagnosis due to a lack of "classic symptoms" in this age group. Tongue lolling, whereby the tongue is positioned in a partially protruded position at rest, was more frequent in younger patients and was

Table 3—Demographic and sleep disorder features compared across the 3 age groups.

	Age Groups			Diff Between Groups *P*
	≤ 12 (n = 18)	13–17 (n = 24)	≥ 18 (n = 12)	
Demographics/anthropometrics n = 54				
†Age	10 (3)	14 (3)	28 (15)	NA
Body mass index (z-score)	1.7 (1.1)	1.2 (1.0)	1.1 (0.9)	.201
†Female	9 (50)	14 (58)	4 (33)	.390
Narcolepsy features n = 54, unless otherwise stated				
†Vaccine related onset	14 (78)	18 (75)	8 (67)	.605
†Excessive daytime sleepiness	18 (100)	24 (100)	12 (100)	1.000
†Cataplexy	17 (94)	20 (83)	10 (83)	.579
†Hypnogogic hallucinations	3 (17)[a]	11 (46)[a,b]	8 (67)[b]	.018
†Sleep paralysis	0 (0)[a]	9 (38)[b]	9 (75)[b]	< .0005
†How many of the core 4 symptoms were present				.002
1	1 (6)[a]	1 (4)[a]	1 (8)[a]	—
2	14 (78)[a]	11 (46)[a,b]	2 (17)[b]	—
3	3 (17)[a]	7 (29)[a]	2 (17)[a]	—
4	0 (0)[a]	5 (21)[a,b]	7 (58)[b]	—
†Diagnostic delay (weeks)	112 (68)	104 (86)	160 (358)	.06
†Time-lag postvaccine to symptom onset (weeks) (n = 41)	52 (75)	23 (35)	31.5 (63)	.383
Possible prior risk factor (other than vaccination)	6 (33)	13 (954)	5 (42)	.409
Sleep disorder symptoms n = 54, unless otherwise stated				
Daytime napping (n = 52)	18 (100)	22 (96)	11 (100)	1.000
Number of naps per day				.971
≤ 1	5 (28)	5 (21)	2 (17)	—
2	6 (33)	9 (38)	5 (42)	—
≥ 3	7 (39)	10 (42)	5 (42)	—
Zoning out/reduced attention	15 (83)	23 (96)	11 (92)	.423
Reduced work/school performance	8 (44)	15 (63)	9 (75)	.251
Vivid dreams (n = 53)	13 (72)	20 (87)	12 (100)	.100
Nightmares (n = 53)	9 (50)	13 (57)	6 (50)	.882
Excessive nocturnal waking	15 (83)	17 (71)	10 (83)	.638
Excessive irritability after napping (n = 42)	10 (67)[a]	12 (60)[a]	0 (0)[b]	.007
Increased weight (n = 52)	10 (59)	9 (39)	4 (33)	.373
Reduction in physical activity (n = 53)	7 (39)	8 (35)	6 (50)	.717
Sleep talking	12 (67)	13 (54)	3 (25)	.076
Sleep shouting (n = 53)	5 (29)	4 (17)	1 (8)	.393
Cataplexy features n = 45, unless otherwise stated				
Laughter induced	15 (100)	17 (85)	9 (90)	.329
Neck weakness	9 (60)	17 (85)	8 (80)	.233
Facial muscle weakness	9 (60)	17 (85)	6 (60)	.172
Tongue protrusion	5 (33)	4 (20)	0 (0)	.113
Falls	4 (27)	5 (25)	4 (40)	.700
Emotionally upset after cataplexy	5 (33)	7 (35)	2 (20)	.774
Lolling (n = 52)	9 (50)[a]	5 (22)[a,b]	0 (0)[b]	.007
Cataplexy frequency (n = 44)	—	—	—	.013
≤ 1 per day	6 (40)	8 (40)	2 (22)	—
1–2 per day	4 (27)	13 (60)	2 (33)	—
≥ 3/variable	5 (33)[a]	0 (0)[b]	4 (44)[a]	—

Data presented as mean (standard deviation), †median (interquartile range) and frequency (%) as appropriate. [a,b]Each superscript letter identifies a group whose values do not differ from each other. NA = not applicable.

Table 4—Investigation results compared across the 3 age groups.

	Age Groups			Diff Between Groups *P*
	≤ 12 (n = 18)	13–17 (n = 24)	≥ 18 (n = 12)	
Ancillary investigation results				
HLA typing (n = 41), DQB1 06*02 positive	14 (100)[a,b]	21 (100)[b]	4 (67)[a]	.018
Hypocretin testing (n = 24)				
< 50 pg/L	9 (82)	12 (92)	0 (0)	.576
50–110 pg/L	2 (18)	1 (7)	0 (0)	
Neuroimaging (n = 46), abnormal	2 (11)	3 (13)	3 (43)	.138
PSG/MSLT results n = 54, unless otherwise stated				
†PSG sleep latency (min)	7.5 (12.3)[a,b]	7 (10.8)[a]	21 (25.3)[b]	.015
†PSG REM latency (min)	71.5 (151.5)	62.0 (90.8)	66.0 (77.0)	.865
PSG nSOREMP (yes)	7 (39)	10 (42)	3 (25)	.713
†MSLT latency (min)	1.75 (1.0)[a]	2.0 (1.9)[a,b]	4.0 (4.0)[b]	.011
†MSLT number of SOREMPs	4 (1)	4 (0)	4 (1)	.194
†AHI	2 (2)	2 (3)	3 (4)	.606
†Periodic leg movements of sleep index	7 (10)	7 (7)	7 (10)	.914
†Leg jerks index (n = 53)	17 (13)	16 (11)	12.5 (18)	.619
†Stage N1 sleep (min)	70 (57)	68.5 (22)	73.5 (35)	.891
†Stage N1 sleep %	14.5 (9)	16.5 (6)	16.5 (8)	.694
†Stage N2 sleep (min)	186.5 (106)	196.5 (41)	212 (45)	.694
†Stage N2 sleep %	41 (17)	43 (6)	44.5 (8)	.215
Stage N3 sleep (min)	117.6 (28.5)	94.9 (20.2)	67.6 (24.8)	< .0005
Stage N3 sleep %	24 (5.6)	21.3 (4.3)	15.3 (5.9)	< .0005
REM sleep (min)	79.4 (30.2)	84.0 (27.6)	97.5 (35.4)	.273
REM sleep %	16.2 (6.4)	18.6 (5.7)	21.3 (6.0)	.08
Total sleep time (min)	487.5 (55.6)	448.8 (53.4)	451.7 (67.5)	.084
†Number of REM sleep periods (n = 48)	4.5 (2)	5 (1)	5 (1)	.923
†Wake after sleep onset (min) (n = 53)	59.5 (49)	46.5 (74)	47 (43)	.495
†% Sleep efficiency	89.5 (8)	90.5 (12)	89.5 (7)	.726
Awake index (n = 48)	4 (2)	4.2 (2.2)	3.3 (1.6)	.457
Arousal index (n = 49)	16.5 (7.7)	18.1 (5.7)	19.4 (6.9)	.513
Heart rate (n = 48)	81.3 (14.9)	70.8 (9.2)	66.3 (7.7)	.002
†Delta *R*-R (n = 48)	0.5 (0.3)	0.7 (0.4)	0.6 (0.2)	.513

Data presented as mean (standard deviation), †median (interquartile range), and frequency (%) as appropriate. [a,b]Each superscript letter identifies a group whose values do not differ from each other. AHI = apnea-hypopnea index, Delta *R*-R = median heart rate variability, HLA = human leukocyte antigen, MSLT = Multiple Sleep Latency Test, nSOREMPs = nocturnal sleep onset rapid eye movement periods, pg/L = picogram per liter, PSG = polysomnography, REM = rapid eye movement.

not seen in adults. It would appear to be part of the initial hypotonia seen in childhood narcolepsy. While this lolling of the tongue in children was obvious, even during consultations, other manifestations of childhood hypotonia in narcolepsy, as described by Pizza et al,[28] were not picked up during clinic interviews. Many of our interviews/assessments, however, predate the Pizza et al descriptive report. Tongue protrusion during laughter-provoked cataplexy events appeared to be a different phenomenon; 1 child with cataplexy tongue protrusion did not have lolling and 5 children with lolling did not have tongue protrusion. Of those with tongue lolling (n = 14), 13 had definite cataplexy and 1 did not. The frequency and severity of other typical cataplexy features did not vary between age groups.

In terms of metabolic disturbances, precocious puberty was not observed in any of our cohort, but weight gain was noted in 44%. Despite this, the mean BMI was within normal limits for adults (23.4 kg/m^2) at the time of initial assessment. This compares to 26 kg/m^2 and higher in other studies.[33–35] Weight gain is generally at its most marked early in the condition,[28] and many of our patients have since gained weight. Between-group measurements revealed no difference in BMI *z*-score between age groups.

Polysomnography findings in patients with narcolepsy have consistently demonstrated frequent brief awakenings and arousals in comparison to healthy individuals.[36] This includes increased transitions to wakefulness or stage N1 sleep from deeper sleep stages, and therefore persons with narcolepsy

spend more time in stage N1 sleep, have higher wake time arousal after sleep onset, and overall reduced sleep efficiency.[36] In our cohort, sleep was very fragmented in all patients, and across all age groups. The awake index of 3.3–4.2 events per hour of sleep, the microarousal index of 16.5–19.4 events per hour of sleep, and the sleep efficiency of 89.5% to 90.5% were comparable to those found in other PSG studies of narcolepsy.[36–39] Our patients showed a similar amount of time in stage N1 sleep (14.5% to 16.5%) compared to other studies.[36–38] Wake time arousal after sleep onset was also similar to that reported elsewhere.[36,37] As expected, children ≤ 12 years had more stage N3 sleep (% and minutes) and higher mean heart rate. There was a trend for adults to have less total sleep time. No other PSG findings differed across age groups.

Every patient underwent MSLT and the median sleep latency (2 minutes) and median number of SOREMPs (4) were similar to other studies.[35,40] MSLT results varied with age; children ≤ 12 years had a median sleep latency of 1.75 minutes compared to 4 minutes in adults. The median number of SOREMPs was 4 in all age groups. We had no technical difficulties with MSLT recording in children. These findings suggest that in experienced hands, the MSLT is an accurate diagnostic test for NT1 in young children.

Similar to other studies, the median apnea-hypopnea index was low (2 events/h).[41,42] Sleep fragmentation contributes to breathing abnormalities, especially central events. These findings are similar to recent reports stating that obstructive sleep apnea in pediatric NT1 patients is a rare, mild comorbidity despite high BMI.[14,41]

Increased EMG tone

The EMG results were interesting as not only were patients having phasic increases in EMG tone during REM sleep, when muscle atonia should be present, but the legs were still active during the last REM cycle, in contrast to restless legs syndrome patients, when a progressive decrease in leg jerks overnight is normally seen.[43] Findings are similar to other studies and may help in patients where there is diagnostic uncertainty.[44,45]

Comparing patients with vaccine-related narcolepsy to sporadic narcolepsy

Our second aim was to compare the clinical characteristics of patients with vaccine-related and sporadic narcolepsy. Based on a recent meta-analysis we used a cut-off of 2 years to determine vaccine-related narcolepsy.[46] Few studies have investigated the differences between vaccine-related narcolepsy and sporadic narcolepsy.[17,25,47,48] Minor differences between the 2 groups were noted in a study from 14 centers across France (2013) and in a joint Finnish-Italian study (2014), but there was no emerging theme.[17,47] There are limitations worth noting in these studies. For example, in the Finnish-Italian study, the 2 groups were not contemporaneous, they were from different geographical and cultural backgrounds and were obviously studied in different laboratories. Similarly, an English study on the same topic compiled data from 16 different sleep laboratories and only investigated children.[48] Lastly, another Finnish study with larger numbers (2015) compared its results to a sporadic group that had been investigated as far back as 2002.[25] We chose to include patients of all ages who presented during the same time period to allow a direct, contemporaneous comparison in a single setting.

Between the sporadic and vaccine-related patients, there were no significant differences in the proportions of patients with cataplexy, sleep paralysis, hypnagogic hallucinations, vivid dreams/nightmares, or sleep fragmentation. In both groups, sleep was very disturbed; 36% of sporadic and 58% of vaccine-related patients reported sleep talking, and 25% of the vaccine-related patients had sleep shouting. The only difference between the 2 groups was that a higher proportion of vaccine-related patients were irritable upon awakening from a nap compared to sporadic patients (65% vs 18%, $P = .022$). In the age-group analysis, irritability upon wakening was more frequent in children and teenagers. A logistic regression analysis was performed to determine the independent contributions of age and vaccination status to irritability upon waking. Vaccination status, but not age group, was associated with an increased odds-ratio (OR) of irritability upon waking (OR 8.1; 95% CI 1.3–50.4, $P = .025$). Without a control group it is not possible to determine if the excess of irritability upon wakening in children was driven by narcolepsy or another feature.

In both groups, cataplexy was classic, most patients reporting that it was laughter-induced, and primarily affected face and neck muscles. Falls were uncommon. There was no difference in BMI noted between the groups, nor was there any difference in the proportion reporting weight gain. This is in contrast to Winstone et al, who reported a significantly greater proportion of vaccine-related patients with weight gain, but it is similar to Dauvilliers et al, who reported equal rates of weight gain, and to Pizza et al, who reported equal BMI across groups.[17,47,48] Although physical activity was similar in both groups and relatively stable, with less than half of the vaccine-related group reporting a reduction in activities post-vaccination, the burden of illness is known to be cumulative over time and all of our patients were initially assessed quite soon after the onset of their symptoms.

We also examined the frequency of the "classical" tetrad of symptoms at diagnosis and found that vaccine-related and sporadic patients had similar proportions, with 2, 3, or 4 symptoms identified at first assessment. Time from symptom onset to assessment/diagnosis was similar in both groups. These findings do not support the idea that vaccine-related narcolepsy is either more severe or more abrupt.[14] Pizza and colleagues performed comprehensive studies of children with sporadic narcolepsy and concluded that children frequently demonstrate an abrupt onset followed by an improvement over time.[28,47] Therefore, while the post–H1N1 vaccination period was marked by a surge in cases of narcolepsy,[15] with apparently abrupt onset,[14] this sudden onset was not, in fact, unique to post-vaccination narcolepsy. What was unique during this study period was that many more patients were presenting and being assessed in the earlier stages of the condition than had hitherto been the case.

The lack of any major clinical differences between the sporadic and vaccine-related patients is supported by the PSG and MSLT findings. The 2 groups had similar stage N1, stage N3, and REM sleep times, but vaccine-related patients spent a longer time in stage N2 (210 vs 182 minutes, $P = .042$). Sporadic patients tended to spend a greater proportion of their sleep in wakefulness after sleep onset (62 vs 43 minutes), although this

difference was not statistically significant. The number of nocturnal sleep onset REM periods (SOREMPs, ≤15 minutes) was similar in both groups, in contrast to Dauvilliers and colleagues who found more SOREMPs in their vaccinated group.[17] Alakuijala and colleagues noted a shorter sleep latency and more SOREMPs in vaccinated patients but this difference disappeared once the data was adjusted for age.[25]

Cerebrospinal fluid hypocretin levels and rates of HLA DQB*0602 positivity were similar between groups. With respect to other populations with vaccine-related narcolepsy, it has been reported that 100% of patients bore this allele, but it was slightly less in our group, even though 1 vaccine-related patient had cataplexy.[14,16] Unfortunately, hypocretin levels are not available for this patient. When both were available, MSLT results and hypocretin levels were concordant with respect to the diagnosis in all patients. While both tests are excellent for diagnosis, they do not have prognostic value for the burden of illness or response to treatment. Where tested, the hypocretin levels were < 50 pg/mL in almost every patient, and lower levels were not associated with a more severe phenotype, as noted by Sarkanen and colleagues.[49]

In addition to influenza H1N1 vaccination, circulating upper airway pathogens have been proffered as immunogenic triggers leading to the onset of narcolepsy, particularly in children.[20,30,42] ASO titers were not routinely carried out; however, the commonest previous illnesses were related to the upper airway. There was a trend for the presence of more priming factors in the sporadic group (P = .081), as expected. Watson et al previously reported that narcolepsy risk was associated with higher birth order, ie, second-born or subsequent children, who are genetically susceptible and have a higher risk of developing narcolepsy, perhaps reflecting the effects of environmental factors within the family unit.[50] This however was not borne out in our study.

The exact duration of increased risk of narcolepsy following influenza A (H1N1) vaccination is unknown. A recent meta-analysis outlined the evidence for an increased risk in the first year after vaccination and suggested caution when extending risk into the second year.[46] In a sensitivity analysis, we dichotomized our vaccine-related cohort based on the median time to symptom onset and compared patients in whom symptoms developed within 26 weeks of vaccination to those with a longer latency, and also compared them to sporadic patients. We found no evidence that the "early presenters" were more severe or different in any other way to the "late presenters" (all Ps > .05, data not shown). This suggests that the pathophysiology of narcolepsy is likely to be similar in all patients.

Strengths and limitations

The major strength of this study is that it provides a comprehensive cross-sectional overview of the clinical characteristics of patients recently diagnosed with sporadic and vaccine-related narcolepsy in 1 center, who were seen during the same time period and by the same medical team.

Limitations of our study include the lack of an age-matched control group, such as other patients referred to the center with excessive daytime sleepiness, and the relatively small number of sporadic patients. This unfortunately was inevitable as we wanted our groups to come from the same time period.

CONCLUSIONS

In conclusion, the literature to date has reported minor and often conflicting differences in the distinguishing features of vaccine-related vs sporadic narcolepsy. Our study supports existing evidence that patients with vaccine-related narcolepsy do not differ significantly from those with sporadic narcolepsy in terms of clinical features, sleep study findings, cerebrospinal fluid hypocretin levels, or HLA-DBQ*0602 positivity. What distinguishes patients with vaccine-related narcolepsy in Ireland, however, is that, over the period of time this study encompasses, they were much more numerous than patients with sporadic narcolepsy. A sudden surge of patients may lead to the belief that the cases are different, but the objective evidence does not support this impression.

ABBREVIATIONS

ASO, anti-streptolysin O
BMI, body mass index
EMG, electromyography
HLA, human leucocyte antigen
MSLT, Multiple Sleep Latency Test
NT1, narcolepsy type 1
PSG, polysomnography
REM, rapid eye movement
SOREMP, sleep onset rapid eye movement period

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ACKNOWLEDGMENTS

The authors thank Lisa Slattery (narcolepsy nurse specialist) for her help with sourcing data.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May 28, 2020
Submitted in final revised form November 24, 2020
Accepted for publication November 24, 2020
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DISCLOSURE STATEMENT

All authors have read and approved the enclosed document. Work for this study was performed at the authors' respective institutions. The authors report no conflicts of interest.