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Brief Communication

Childhood narcolepsy with cataplexy: comparison between post-H1N1 vaccination and sporadic cases

Fabio Pizza [a,b], Hanna Peltola [c], Tomi Sarkanen [c], Keivan K. Moghadam [a,b], Giuseppe Plazzi [a,b], Markku Partinen [c,*]

[a] Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy
[b] IRCCS Istituto delle Scienze Neurologiche di Bologna, AUSL di Bologna, Bologna, Italy
[c] Helsinki Sleep Clinic, Vitalmed Research Centre, Helsinki, Finland

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ABSTRACT

Objectives: We aimed to compare post-Pandemrix® vaccination (postvaccine) childhood narcolepsy with cataplexy (NC) vs sporadic pre-H1N1 pandemic (pre-H1N1) cases.
Methods: Clinical, anthropometric, polysomnographic, and cerebrospinal hypocretin 1 (hcrt-1) measurements were collected together with the video recordings of cataplexy in 27 Finnish patients with NC onset after H1N1 Pandemrix® vaccination (mean age, 12 ± 4 years; 52% boys) and 42 Italian NC patients with NC onset before the H1N1 pandemic (mean age, 11 ± 3 years; 48% boys). All subjects carried the HLA-DQB1∗0602 allele.
Results: Postvaccine subjects were older at NC onset (12 ± 3 vs 9 ± 3 years; $P = .008$) and displayed a shorter mean sleep latency in multiple sleep latency tests (MSLT) (2.3 ± 2.2 vs 3.7 ± 2.9 min; $P = .026$) compared to pre-H1N1 cases. Anthropometric, clinical (core NC symptoms), hcrt-1 deficiency, and polysomnographic data did not differ among groups, but higher disrupted nocturnal sleep was observed in postvaccine subjects. Comparison of cataplexy features at video assessment showed an overlapping picture with the exception for hyperkinetic movements which appeared to be more evident in pre-H1N1 subjects.
Conclusions: The clinical picture of childhood NC was similar in postvaccine and pre-H1N1 children.
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1. Introduction

Narcolepsy with cataplexy (NC) is a chronic sleep disorder linked to the loss of hypocretin-producing neurons located in the posterolateral hypothalamus, and it is characterized by symptoms of rapid eye movement sleep dissociation [1]. Mounting scientific evidence suggest that NC etiology is linked to an autoimmune attack of the brain triggered by environmental triggers (e.g., streptococcal infection) [2] in subjects carrying the HLA-DQB1∗0602 allele [3]. In the beginning of 2010, several new diagnoses of NC in children and adolescents were made in Finland and Sweden. An association between AS03 adjuvanted H1N1 vaccination (Pandemrix®) and NC was observed, and the Finnish authorities decided to cease vaccinations until further proof was obtained regarding the safety of the vaccine. The increase in the incidence of NC in children aged less than 17 years was 17-fold compared to previous years [4], and the attributable risk for narcolepsy in those aged between 4 and 19 years after having the vaccination was 1 out of 16,000 [5]. On the other hand, a transient abrupt increase of childhood NC occurred in association with the H1N1 pandemic without vaccinations in Northern China [6,7]. Further epidemiologic studies have verified that there is an association with the Pandemrix® vaccination and narcolepsy, especially in individuals aged less than 20 years [4,5,8–10].

Given the genetic and immunologic similarities between the 1918 Spanish and 2009 H1N1 influenza viruses, these new childhood cases suggest a different phenotype, possibly reflecting a wider encephalitic damage of the central nervous system compared with sporadic NC. Therefore, the aim of our study was an all-around clinical comparison between children who developed NC after Pandemrix® vaccination vs sporadic pre-H1N1 pandemic NC cases.

2. Methods

We compared the clinical features of post H1N1 Pandemrix® vaccination (postvaccine) and sporadic childhood NC (pre-H1N1) from 27 HLA-DQB1∗0602–positive children who developed NC after

∗ Corresponding author. Address: Helsinki Sleep Clinic, Vitalmed Research Centre, Sitratori 3, 00420 Helsinki, Finland. Tel.: +358 50 560 4999; fax: +358 9 440 260.
E-mail addresses: markku.partinen@helsinki.fi, markpart@me.com (M. Partinen).

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Pandemrix® vaccination (onset occurring between the years of 2009 and 2011), diagnosed in Helsinki, vs 42 HLA-DQB1∗0602-positive children who developed NC before the H1N1 pandemic (symptoms onset before the year 2010), diagnosed in Bologna. The study was approved by local review boards and written parental informed consent and subjects' assent were obtained in all cases.

During diagnostic procedures, subjects and parents underwent a systematic clinical interview focusing on the presence and timing of the following complaints: excessive daytime sleepiness (EDS) (assessed with the Pediatric Daytime Sleepiness Scale), cataplexy, sleep paralyses, sleep hallucinations, disturbed nocturnal sleep, and aggressive behavior or irritability. Anthropometric data were collected (height, weight) to calculate the body mass index (BMI) and BMI percentile in comparison with the World Health Organization growth percentile scales for boys and girls to define obesity (BMI >97th percentile), overweight (BMI between the 85th and 97th percentiles), and normal weight (BMI <85th percentile).

Diagnostic assessment included nocturnal polysomnographic recording followed by multiple sleep latency test (MSLT) with either 4 or 5 nap opportunities [11], and lumbar puncture for cerebrospinal hypocretin-1 (hcrt-1) measurement performed whenever possible (Human orexin-A RIA Kit, Phoenix Pharmaceutical, Inc., Belmont, CA) [1]. Brain magnetic resonance imaging study was performed in all subjects. Finally, subjects were video recorded while watching funny videos to elicit cataplexy whenever possible, and a blinded observer (P.H.) scored the presence of hypotonic and active motor features, as previously described [12] in two subgroups of age- and sex-matched subjects.

Data were explored using descriptive statistics for each subject's group (mean ± standard deviation or percentages for continuous or categorical variables), and nonparametric statistical comparisons were performed with Mann–Whitney and χ^2 tests as appropriate. MSLT data were standardized by calculating the mean sleep latency of the first four naps for all subjects and the percentage of sleep-onset rapid eye movement periods (SOREMPs) over the recorded naps. A P value <.05 was considered statistically significant.

3. Results

Data of the two subject populations are reported in Table 1. Subjects were comparable in age at observation; postvaccine cases were reported as the onset of the first NC symptom at older age and were observed after a shorter time from onset of the first symptom (either sleepiness or cataplexy). The representation of clinical symptoms (EDS, cataplexy, sleep paralyses or hallucinations, and aggressive behavior or irritability) was comparable among groups, but the postvaccine subjects more frequently reported disrupted nocturnal sleep with frequent awakenings. The mean BMI did not differ between groups, despite a nonsignificant trend towards overweigh and obesity in pre-H1N1 vs postvaccine cases.

Nocturnal sleep features were similar in the two populations; however, postvaccine subjects showed a shorter mean sleep latency than pre-H1N1 cases despite comparable subjective sleepiness severity. All subjects were hcrt-1 deficient (i.e., <110 pg/mL) and revealed no abnormalities on brain magnetic resonance imaging.

Table 1
Clinical and polysomnographic features of pre-H1N1 Italian and postvaccination Finnish children with narcolepsy and cataplexy.

	n	Italy: pre-H1N1 NC		*n*	Finland: post-H1N1 vaccine NC		*P* value
		Mean or%	SD		Mean or%	SD	
Clinical data							
Boys (%)	42	47.6		27	51.6		.731
Age at NC onset (y)	42	9.36	2.91	27	11.61	3.45	**.008**
Age at NC diagnosis (y)	42	11.48	3.30	27	12.29	3.58	.369
Diagnostic delay (y)	42	1.91	2.11	27	0.68	0.44	**.001**
Weight (kg)	39	49.96	16.29	21	52.37	20.11	.959
Height (meters)	39	1.50	0.18	21	1.57	0.20	.279
BMI (kg/m^{-2})	39	21.69	3.57	21	20.43	3.29	.178
BMI (normal, overweight, obese) (%)	39	28.2; 71.8		21	52.4; 47.6		.064
NC symptoms							
Excessive daytime sleepiness (%)	42	100		27	100		1.000
Excessive daytime sleepiness: onset age	42	9.38	2.94	27	11.61	3.63	**.009**
Cataplexy (%)	42	100		27	96.3		.209
Cataplexy: onset age	41	10.11	3.06	27	11.80	3.37	.066
Sleep paralysis (%)	38	26.3		27	37.0		.356
Sleep paralysis: onset age	9	9.78	4.79	0	N.A.		N.A.
Hypnagogic hallucinations (%)	38	60.5		27	55.6		.689
Hypnagogic hallucinations: onset age	23	10.40	3.45	0	N.A.		N.A.
Disturbed nocturnal sleep (%)	38	52.6		21	77.8		**.038**
Disturbed nocturnal sleep: onset age	19	9.68	3.05	0	N.A.		N.A.
Aggressive behavior/irritability (%)	32	59.4		22	45.5		.313
Pediatric daytime sleepiness scale (*n*)	34	14.85	3.49	20	15.30	3.79	.461
Polysomnographic data							
Nocturnal total sleep time (min)	42	483.02	86.83	15	434.04	128.89	.080
Nocturnal sleep efficiency (%)	42	87.35	13.35	16	88.74	7.31	.957
Nocturnal sleep latency	42	6.05	4.10	12	4.78	3.70	.211
Nocturnal REM sleep latency	42	34.18	53.52	12	48.77	53.24	.202
MSLT: mean sleep latency (first four naps)	42	3.75	2.86	26	2.33	2.16	**.026**
MSLT: SOREMPs (% of naps)	42	82.86	18.51	26	81.73	24.21	.952
HLA typing and CSF hypocretin 1							
Positive DQB1-06:02 (%)	42	100		26	100		1.000
CSF hypocretin 1 < 110 pg/mL (%)	29	100		19	100		1.000

Abbreviations: NC, narcolepsy with cataplexy; *n*, number of subjects; SD, standard deviation; y, years; BMI, body mass index; N.A., not available; min, minutes; REM, rapid eye movement; MSLT, multiple sleep latency tests; SOREMPs, sleep-onset rapid eye movement periods; CSF, cerebrospinal fluid. Bolded text, statistically significant (P<0.05).

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