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Original Article

# Polysomnographic and actigraphic characteristics of patients with H1N1-vaccine-related and sporadic narcolepsy

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ABSTRACT

*Objective:* After the pandemic H1N1 influenza ASO3-adjuvanted vaccine, Pandemrix©, was used in late 2009 and early 2010, the incidence of narcolepsy increased in many European countries. This incidence mainly increased in children and adolescents and, to a lesser degree, in adults.
*Patients/Methods:* 125 unmedicated patients, aged 4 to 61 years, were included in this case-series study. Of these, 69 were diagnosed to have an H1N1-vaccine-related narcolepsy and 57 had sporadic narcolepsy. Most of these patients had: an actigraphy recording of 1–2 weeks, polysomnography, a Multiple Sleep Latency Test (MSLT), and cerebrospinal fluid hypocretin-1 concentration analysis.
*Results:* Patients with H1N1-vaccine-related narcolepsy had shorter diagnostic delays, lower periodic leg movement index during sleep, earlier sleep–wake rhythm, and were younger in age at diagnosis, compared with sporadic cases. They also had shorter sleep latency and more sleep onset REM periods in MSLT, but these results were strongly age-dependent. Actigraphy showed quantitatively less sleep and more sleep fragmentation than polysomnography.
*Conclusion:* Regarding polysomnographic and actigraphic characteristics, there were no dramatic deviations between H1N1-vaccine-related and sporadic narcolepsy. Circadian rhythms indicated some interesting new findings with respect to the H1N1-vaccine-related disease. An actigraphy recording of 1–2 weeks is useful when studying the nocturnal aspects of narcolepsy and sleep–wake rhythms of narcoleptic patients.



## 1. Introduction

Narcolepsy is a rare sleep disorder that is characterized by excessive daytime sleepiness (EDS) and irresistible attacks of falling asleep, even in active situations. A specific phenomenon of narcolepsy is cataplexy, which is a sudden episode of loss of muscle tone triggered by emotions; a minority of narcolepsy patients never develops unambiguous cataplexy. Narcolepsy without cataplexy is a challenge in diagnostics and may comprise many separate subtypes [1]. Narcolepsy with cataplexy is, in most cases, linked to hypocretin-1 (orexin-A) deficiency in cerebrospinal fluid (CSF).

After the pandemic H1N1 influenza ASO3-adjuvanted vaccine, Pandemrix©, was used in late 2009 and early 2010, the incidence of narcolepsy increased in many European countries [2–11]. Initially, the increase in the incidence of narcolepsy was noticed mainly in children and adolescents aged less than 20 years [5,6]. Later on, it was shown that the risk also increased in adults [7,12,13], albeit less than in younger age groups. However, the incidence of narcolepsy in children increased after the H1N1 influenza pandemic in China, where no H1N1 vaccine was used, which suggests that the H1N1 virus itself could also trigger narcolepsy [14,15].

Previously, narcoleptic patients have been shown to have more awakenings during their night sleep than control subjects [16,17]. Sleep efficiency in polysomnography (PSG) is usually within normal range, but often slightly reduced compared with healthy subjects [16]. Sleep latency and rapid eye movement (REM) sleep latency are often shortened [7,18–20]; the latter is thought to be a strong diagnostic marker for narcolepsy [19].

So far, only two groups have published detailed comparisons for clinical picture and sleep study characteristics between vaccine-exposed

*Abbreviations:* ACT, actigraphy; AHI, apnea–hypopnea index; BMI, body mass index; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; HLA, human leukocyte antigen; L5, lowest 5; M10, maximal 10; MSLT, Multiple Sleep Latency Test; PLMSI, periodic leg movement index during sleep; PSG, polysomnography; RBD, REM sleep behavior disorder; RLS, restless legs syndrome; SOREMP, sleep onset REM period.

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and non-exposed narcolepsy cases: one study was on French children and adults [7], and the other was between Italian children with sporadic pre-H1N1 narcolepsy and Finnish children with post H1N1-vaccination narcolepsy [21]. Chinese children with the onset of narcolepsy following the winter 2009–2010 H1N1 influenza pandemic were also compared to narcolepsy cases with onset before or after the pandemic [22].

Previously, very few studies about actigraphic data specifically for narcolepsy patients have been published. Two groups studied the effects of treatment for narcolepsy on daytime inactivity of the patients [23,24]. Actigraphy (ACT) was also shown to be able to discriminate between narcoleptics and controls, based on the quantity of diurnal inactivity [24,25]. When nightly sleep duration of subjects with EDS, but not necessarily narcolepsy, was measured by ACT and sleep logs during a fortnight preceding the Multiple Sleep Latency Test (MSLT), it was discovered that sleep latency in MSLT correlated with actigraphy-measured sleep quantity but not with self-reported sleep duration; based on actigraphic data, many subjects reported to have slept much more than was possible [26].

With sleep-disordered patients in general, total sleep time and sleep efficiency were essentially similar when simultaneous actigraphic and polysomnographic data were compared [27,28]. Moreover, ACT is an excellent tool for assessing sleep phase disorders [29]. Wrist activity, measured by ACT, has shown to be a strong correlate of endogenous melatonin release and the circadian phase [30].

In the present study, the aim was to compare the characteristics of MSLT, PSG, and ACT among H1N1-vaccine-related and sporadic narcolepsy patients.

## 2. Materials and methods

The Helsinki and Uusimaa Ethics Committee approved the present study. Most results were obtained during normal diagnostic procedures. Written informed consent to use their data was received from all patients; this was also for studies that were not part of the diagnostic procedure. Parents signed the written informed consent on behalf of the children involved in the present study.

A total of 125 unmedicated narcolepsy patients, with the available data from MSLT and PSG and/or ACT, were included in the present case-series study. Of those, 69 (55%) were diagnosed to have an H1N1-vaccine-related narcolepsy. They had all been vaccinated between October and December 2009 with Pandemrix©, and their symptoms (in most cases EDS, but in some cases cataplectic attacks) started, on average, 94 days after the vaccination. Median delay from the vaccination to the symptoms was 69 days and 94% had a delay of less than 240 days. Those four patients who had a longer delay (242–479 days) between the vaccination and the onset of the disease were judged to have a vaccine-related narcolepsy because they fulfilled both the ICSD-2 criteria [31] and the Brighton criteria [1], there were no other causal factors of symptoms, and their previous medical history revealed no sleepiness or cataplexy before the vaccination. Of the 125 patients with narcolepsy, 57 had narcolepsy that was not related to vaccination. Their symptoms started either before (72%) or clearly after (more than 550 days in all cases) (28%) the above mentioned time period, even if 58% of them got vaccinated as well. The collection of information and verification of narcolepsy diagnoses were described previously in more detail [6].

In the present study, the diagnoses was made between 2002 and 2012. Since 2005, the narcolepsy diagnosis was made and MSLT was performed according to the ICSD-2 criteria [31,32]. The number of MSLT sessions varied between four and five, with an average of 4.29. Occasionally, the fifth session was omitted, had there already been two or more sleep onset REM periods (SOREMPs) during the first four sessions. Only those who had a mean sleep latency of less than or equal to 8 min in MSLT and two or more SOREMPs in four or five MSLT sessions were included, unless a CSF hypocretin-1 concentration under 110 pg/mL verified the diagnosis. Analysis of CSF hypocretin-1 concentration was preformed at the Rinnekoti Research Centre (Orexin A RIA kit, Phoenix Pharmaceuticals, San Mateo, CA, USA). Sleep stages, breathing, and leg movements were scored manually according to international criteria [33,34].

The ACT recordings lasted for a week or a fortnight, and analyses were done using Actiwatch® (Cambridge Neurotechnology Ltd, Cambridgeshire, UK). The subjects or their parents always filled in a sleep log, which was combined with the recordings. The epoch length was 1 min and the sensitivity of the algorithm for wake threshold was set to the medium sensitivity.

The definitions of the used ACT parameters were as follows: sleep latency – the difference between bed time and sleep start (as set by the researcher or derived automatically from a marked event); actual sleep time – the amount of sleep between sleep start and sleep end, wake time excluded, as determined by the algorithm; sleep efficiency – the percentage of time spent asleep between bed time and getting-up time; number of immobile phases of 1 min – during the sleep period, the number of immobile phases (the epochs where activity scores of 0 were recorded) where the duration of the immobile phase was only 1 min (this parameter describes the fragmentation of sleep); movement and fragmentation index – the percentage of time spent moving (the epochs where activity scores greater than zero were recorded) plus the percentage of immobility phases of 1 min as a proportion of the total number of immobility phases during the sleep period. The ACT parameters are shown as median values, which are more resistant to extreme results than mean values.

The definitions of the used circadian parameters in ACT recording are as follows; Cosine peak – the time of the day when the parametric 24-h fixed period cosinor model of the subject's average diurnal activity profile peaks; Light:dark ratio – the ratio between average activity count during daylight (set as 06:00–18:00) and during 'darkness' (18:00–06:00). As the "light" period begins and ends early, compared with the rhythm of everyday life in modern society, the higher the ratio, the more of a morning person a subject tends to be. L5 onset – the start time of the sequence of the five least-active hours in the 24-h average activity profile. M10 onset – the start time of the sequence of the ten most active hours in the 24-h average activity profile. Relative amplitude – the normalized difference between the most active 10-h period and the least active 5-h period in an average 24-h pattern; higher values indicate a stronger rhythm. The three last parameters are part of nonparametric variables for actigraphic data, and are designed for more accurate descriptions of sleep–wake rhythms, which are actually not sinusoidal by waveform [35,36].

Statistical analyses were performed with a computerized statistical package (IBM SPSS® Statistics 19.0, Armonk, NY, USA). For statistical comparisons of the continuous variables, parametric or non-parametric methods were used according to distribution. The normality of distributions was verified by computing their skewness and kurtosis. All $p$-values were two sided, and the significance level was set at 0.05 throughout. For descriptive purposes, the values were reported as means and standard deviations (SD), in some cases also as medians. Because quite a lot of the measured parameters differed between children and adults, age-adjusted differences were also looked at between the two narcolepsy groups. Multifactorial analyses were performed with linear regression.

## 3. Results

The age of the patients included in the present study varied between 4 and 61 years. The median age was 13 years, and only one patient was over 40 years. The patients with H1N1-vaccine-related narcolepsy were