Original Article

Retrospective multicenter matched case–control study on the risk factors for narcolepsy with special focus on vaccinations (including pandemic influenza vaccination) and infections in Germany

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Objective: Studies associate pandemic influenza vaccination with narcolepsy. In Germany, a retrospective, multicenter, matched case–control study was performed to identify risk factors for narcolepsy, particularly regarding vaccinations (seasonal and pandemic influenza vaccination) and infections (seasonal and pandemic influenza) and to quantify the detected risks.

Methods: Patients with excessive daytime sleepiness who had been referred to a sleep center between April 2009 and December 2012 for multiple sleep latency test (MSLT) were eligible. Case report forms were validated according to the criteria for narcolepsy defined by the Brighton Collaboration (BC). Confirmed cases of narcolepsy (BC level of diagnostic certainty 1–4a) were matched with population-based controls by year of birth, gender, and place of residence. A second control group was established including patients in whom narcolepsy was definitely excluded (test-negative controls).

Results: A total of 103 validated cases of narcolepsy were matched with 264 population-based controls. The second control group included 29 test-negative controls. A significantly increased OR to develop narcolepsy (crude OR [cOR] = 3.9, 95% confidence interval [CI] = 1.8–8.5; adjusted OR [aOR] = 4.5, 95% CI = 2.0–9.9) was detected in individuals immunized with pandemic influenza A/H1N1/v vaccine prior to symptoms onset as compared to nonvaccinated individuals. Using test-negative controls, in individuals immunized with pandemic influenza A/H1N1/v vaccine prior to symptoms onset, a nonsignificantly increased OR of narcolepsy was detected when compared to nonvaccinated individuals (whole study population, BC levels 1–4a: cOR = 1.9, 95% CI = 0.5–6.9; aOR = 1.8, 95% CI = 0.3–10.1).

Conclusions: The findings of this study support an increased risk for narcolepsy after immunization with pandemic influenza A/H1N1/v vaccine.

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1. Introduction

1.1. Clinical picture

Narcolepsy is a disabling disorder characterized by excessive daytime sleepiness (EDS), cataplexy (sudden unilateral or bilateral loss of muscle tone triggered by emotions), fragmented nighttime sleep, sleep paralysis, automatic behavior as well as hypnagogic and hypnopompic hallucinations [1]. Despite tremendous medical progress in this field, there is no curative treatment for narcolepsy.

1.2. Etiology

The underlying cause for narcolepsy with cataplexy (narcolepsy type 1) is the almost complete loss of hypothalamic hypocretin neurons [2,3], whereas in narcolepsy without cataplexy (narcolepsy type 2) a partial loss of hypocretin neurons may be found [4]. Hypocretin deficiency was recently shown to occur immediately after disease onset in human narcolepsy with cataplexy [5].
Narcolepsy type 1 is strongly associated with a specific human leukocyte antigen (HLA) subtype. A total of 98% of the narcoleptic Caucasians carry the DRB1*1501-DQB1*0602 HLA subtype, whereas it is found in only 25%−35% of the Caucasian population [6−9]. A genome-wide association study suggests further genetic polymorphism [10]. This striking HLA association, the presence of autoantibodies against hypocretin or hypocretin neurons [11,12], as well as the polymorphism in the T-cell α locus observed in narcoleptic individuals [13] support the notion that narcolepsy might be an autoimmune disease. In susceptible HLA positive individuals, triggered by environmental factors [14], such as streptococcal infections [15], autoimmunological pathways seem to cause the specific elimination of hypocretin producing neurons.

1.3. Association with pandemic influenza A/H1N1/v vaccination

In August 2010, the German authorities were informed on case reports of confirmed narcolepsy following H1N1 vaccination in children and adolescents from Sweden and Finland, suggesting an association between AS03 adjuvanted pandemic influenza A/H1N1/v vaccination and narcolepsy. In the further course, spontaneous reports on suspected narcolepsy following AS03 adjuvanted pandemic influenza A/H1N1/v vaccination were also received from all over Germany.

In the years after the 2009 influenza A/H1N1 (H1N1) pandemic, several epidemiological studies were published supporting an increased risk of developing narcolepsy following vaccination against pandemic influenza A/H1N1 with the AS03 adjuvanted vaccine Pandemrix® [16−26].

Despite encouraging approaches to investigate how vaccination against pandemic influenza A/H1N1 can lead to destruction of hypocretin neurons [27−30], the pathomechanism is not yet fully understood.

1.4. Pandemic mass vaccination campaign in Germany

In Germany, a mass vaccination campaign against pandemic influenza A/H1N1 was started on 26 October 2009. The majority of vaccinees received the split virion, AS03 adjuvanted pandemic influenza A/H1N1/v vaccine Pandemrix® (GlaxoSmithKline Biologicals, Dresden, Germany), soldiers and a part of the civil servants were immunized with the whole virion, not-adjuvanted A/H1N1/v vaccine Celvapan® (Baxter AG, Orth/Donau, Austria). A minority of German vaccinees may have received other pandemic influenza vaccines abroad. Overall, pandemic influenza vaccination coverage in the German population was low (roughly 8%) [31].

1.5. German Narcolepsy Study

In 2011, the German Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut) in collaboration with the German Sleep Society (Deutsche Gesellschaft für Schlafmedizin und Schlafforschung, DGSM) initiated the German Narcolepsy Study, including a retrospective, multicenter, matched case−control study on the risk factors of narcolepsy (part 1) as well as a retrospective study on the incidence of narcolepsy (part 2). The results of the latter were published elsewhere [32]. Part 1 of the German Narcolepsy Study aimed at identifying risk factors for narcolepsy, particularly regarding vaccinations (seasonal and pandemic influenza vaccination) and infections (seasonal and pandemic influenza). A secondary aim was to detect and describe differences between exposed and unexposed cases.

2. Methods

All German sleep centers registered as accredited at the DGSM were invited by mail to participate in the German Narcolepsy Study (parts 1 and 2).

2.1. Case identification

Participating sleep centers were asked to identify from their patient population individuals referred for multiple sleep latency test (MSLT) between 1 April 2009 and 31 December 2012 with place of residence in Germany, symptom onset (excessive daytime sleepiness) after 31 December 2004, and predefined suspected diagnoses (ICD 10 codes G47.1 Disorders of excessive somnolence [hypersonnias], G47.2 Disorders of the sleep−wake schedule, G47.4 Narcolepsy and cataplexy, G47.8 Other sleep disorders, G47.9 Sleep disorder, unspecified, F51.1 Nonorganic hypersomnia, F51.2 Nonorganic disorder of the sleep−wake schedule, F51.3 Sleep-walking [somnambulism], F51.4 Sleep terrors [night terrors], F51.8 Other nonorganic sleep disorders, F51.9 Nonorganic sleep disorder, unspecified). Patients diagnosed with narcolepsy prior to 1 April 2009 were excluded.

Patients fulfilling the inclusion criteria were contacted by the sleep centers to obtain written informed consent to transcribe recorded data (including demographics, medical history, clinical examinations, and relevant findings regarding sleep disorders) to a standardized case report form (CRF). Within the scope of this CRF, sleep centers were also requested to provide the Epworth Sleepiness Scale (ESS) score, since it was a retrospective study, we did not specify the ESS version but rather the score range (0−24) to be used. In addition, for children and adolescents <16 years, there was also the possibility to provide the Pediatric Daytime Sleepiness Scale (PDSS) with a score range of 0−32 [33].

2.2. Case ascertainment and validation

The CRFs were validated by two independent experts for sleep medicine (G.M. and P.G.) according to the criteria of narcolepsy as an adverse event following immunization (AEFI) defined by the Brighton Collaboration [34] blinded for the patient’s and the sleep center’s identity and the exposures to potential risk factors including vaccination. In case of discrepant expert validations, the experts were asked to re-evaluate the case and to come to an agreement. Case reports fulfilling the criteria of BC levels 1−4a were eligible.

2.3. Population-based controls

Addresses of potential population-based controls were identified by the regional registration offices and transmitted to the study secretary. Potential controls, or in the case of children and adolescents, persons who had custody (usually a parent) were contacted to obtain written informed consent.

2.4. Matching

Cases of narcolepsy were matched with population-based controls by year of birth (±1 year in children and adolescents, ±3 years in adults), gender, and place of residence (first two digits of the zip code) in a ratio of 1:4.

2.5. Test-negative controls

A second control group was established from the patient population fulfilling the inclusion criteria in whom narcolepsy was
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