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Incidence of narcolepsy before and after MF59-adjuvanted influenza A(H1N1)pdm09 vaccination in South Korean soldiers

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ABSTRACT

Background: Previous reports mostly from Europe suggested an association between an occurrence of narcolepsy and an influenza A(H1N1)pdm09 vaccine adjuvanted with AS03 (Pandemrix®). During the 2009 H1N1 pandemic vaccination campaign, the Korean military performed a vaccination campaign with one type of influenza vaccine containing MF59-adjuvants. This study was conducted to investigate the background incidence rate of narcolepsy in South Korean soldiers and the association of the MF59-adjuvanted vaccine with the occurrence of narcolepsy in a young adult group.
Methods: To assess the incidence of narcolepsy, we retrospectively reviewed medical records of suspicious cases of narcolepsy in 2007–2013 in the whole 20 military hospitals of the Korean military. The screened cases were classified according to the Brighton Collaboration case definition of narcolepsy. After obtaining the number of confirmed cases of narcolepsy per 3 months in 2007–2013, we compared the crude incidence rate of narcolepsy before and after the vaccination campaign.
Results: We included 218 narcolepsy suspicious cases in the initial review, which were screened by the diagnostic code on the computerized disease registry in 2007–2013. Forty-one cases were finally diagnosed with narcolepsy in 2007–2013 (male sex, 95%; median age, 21 years). The average background incidence rate of narcolepsy in Korean soldiers was 0.91 cases per 100,000 persons per year. During the 9 months before vaccination implementation (April to December 2009), 6 narcolepsy cases occurred, whereas during the next 9 months (January to September 2010) including the 3-month vaccination campaign, 5 cases occurred.
Conclusions: The incidence of narcolepsy in South Korean soldiers was not increased after the pandemic vaccination campaign using the MF59-adjuvanted vaccine. Our results suggest that the MF59-adjuvanted H1N1 vaccine did not contribute to the occurrence of narcolepsy in this young adult group.

1. Introduction

Narcolepsy is a rare sleep disorder characterized by the recurrent, irresistible need to sleep, with or without cataplexy. In patients with cataplexy in particular, narcolepsy is known to be caused by a hypocretin deficiency resulting from an autoimmune mechanism [1–3]. Although the precise cause of narcolepsy remains unknown, it is believed that an autoimmune process might be triggered by exposure to environmental factors such as infections or vaccinations in genetically susceptible individuals

Abbreviations: DMSIS, Defense Medical Statistics Information System; ICD, International Classification of Diseases and Related Health Problems; SPSS, Statistical Package for the Social Science; IQR, interquartile range; MSLT, multiple sleep latency test; SOREMP, sleep-onset rapid eye movement period; ICSD, International Classification of Sleep Disorders; DSM, Diagnostic and Statistical Manual of Mental Disorders.

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[4,5]. Accordingly, both influenza infections and vaccinations may influence the increase of narcolepsy in a situation such as an influenza pandemic. Several reports have generated concern that an influenza A(H1N1)pdm09 vaccine containing the adjuvant AS03 (Pandemrix®) was associated with an increased risk of narcolepsy in childhood and adolescence [6–13]. In addition to the multinational epidemiological study [14], these concerns have recently been extended to the MF59-adjuvanted H1N1 vaccine and the non-adjuvanted influenza H1N1 vaccine itself [15–17].

During the 2009 pandemic influenza outbreak in South Korea, inactivated monovalent H1N1 vaccine was used with just two types of vaccine formulations, of which one was the nonadjuvanted vaccine (GREENFLU-S®, Green Cross Corp., Hwasoon, South Korea) and the other was the MF59-adjuvanted vaccine (GREENFLU-S plus®; the adjuvant produced by Novartis Vaccines and Diagnostics Inc., Emeryville, CA, USA) [18]. The recipients of the MF59-adjuvanted H1N1 vaccine included adults aged ≥19 years except for healthcare workers, essential social service workers, and pregnant women. In particular, Korean military personnel (623,771 of 750,000; 83.2%) were vaccinated solely with the MF59-adjuvanted H1N1 vaccine between January and March 2010 [18]. Korean soldiers are almost exclusively between 18 and 25 years of age.

A previous study in South Korea did not find increased narcolepsy incidence during the 2009 H1N1 pandemic vaccination campaign [15]. However, the study results were limited to verifying narcolepsy cases that were not reviewed through medical records and to clinical information such as the presence of cataplexy or polysomnography results. Our aim was to examine whether the MF59-adjuvanted H1N1 vaccine was associated with an increased risk of narcolepsy in a young adult group. Through a retrospective chart review, we (1) investigated the background incidence of narcolepsy in Korean soldiers, which is mainly composed of young adults in their late teens and early 20s and (2) compared its incidence before and after the 2009 H1N1 pandemic vaccination campaign using the MF59-adjuvanted vaccine.

2. Methods

2.1. Characteristics of study population

The study population included all active duty soldiers and military officers in the Korean military. In South Korea, military service is mandatory for healthy males older than 18 years. The service period is generally 21–24 months. Annually, more than 300,000 healthy young adults become duty soldiers and a comparable number of soldiers complete their military service. In the Korean military, any soldier who needs to be tested for narcolepsy or its related conditions should at least once visit an outpatient clinic in the one of the 20 military hospitals. Since 2007, a computerized disease registry of all Korean military hospitals (Defense Medical Statistics Information System, DMSIS) has been available.

2.2. Case identification

We retrospectively reviewed the medical records of suspected narcolepsy cases in military hospitals from January 2007 to December 2013. We screened possible cases of narcolepsy with the following diagnostic codes: narcolepsy and cataplexy (G47.4); disorders of excessive somnolence (hypersomnias) (G47.1); nonorganic hypersomnia (F51.1); other nonorganic sleep disorders (F51.8); nonorganic sleep disorder, unspecified (F51.9); other sleep disorders (G47.8); and sleep disorder, unspecified (G47.9), using DMSIS and based on the International Classification of Diseases and Related Health Problems (ICD), 10th revision. Because the diagnostic code of ICD-10 for narcolepsy is limited to "narcolepsy and cataplexy (G47.4)," clinicians may diagnose some narcolepsy cases (e.g., especially without cataplexy) using the other diagnoses codes. Thus, we must have included all possible cases with the previously mentioned diagnostic codes.

2.3. Case classification

By reviewing the screened cases' medical records, two sleep specialists (W.J.K. and S.D.L.) independently classified the diagnostic certainty of each case according to the Brighton Collaboration case definition of narcolepsy [19], and then excluded cases with insufficient evidence to meet the case definition (i.e., level 4–5). Unambiguous cataplexy was determined as follows: (1) sudden and unexpected onset of episodes and (2) concomitant presence of (a) partial/generalized muscle weakness, (b) preserved consciousness during the episodes, and (c) at least two attacks with clear emotional triggers [19]. One additional criterion for defining unambiguous cataplexy – that the duration of each episode lasted less than 30 seconds – could not be applied in the current study because few medical records described attack duration.

2.4. Data analysis

We obtained the raw number of newly diagnosed narcolepsy cases in each 3-month period and per year in 2007–2013. By doing so, we assessed the crude incidence rate of narcolepsy by season, and by year as well. The vaccination campaign against influenza A(H1N1)pdm09, which used only one MF59-adjuvant vaccine, was implemented between January and March 2010 in the Korean military. To compare the incidence of narcolepsy before and after the pandemic vaccination campaign, we defined the prevaccination campaign period as April to December 2009 (9 months) [15,18] and the vaccination campaign (3 months) and the 6 months following as January to September 2010 [6,19,20].

For defining incidence, the date of disease onset was regarded as the first date of a clinical visit related to narcolepsy. In calculating the annual background incidence rates of narcolepsy diagnosis, denominators were calculated as the approximate number of soldiers from the biennial reports of the Korean military as follows: 650,000 in 2007–2008 [21]; 653,000 in 2009–2010 [22]; 636,000 in 2011–2012 [23]; and 639,000 in 2013 [24].

We also examined the demographic and clinical factors of available cases such as follows: sex, age, height, weight, reported symptoms, results of confirmatory tests, psychiatric/neurological comorbidities, and any other significant medical illness. Descriptive analyses of the demographic and clinical factors were conducted using the Statistical Package for the Social Science (SPSS) for Windows, version 20 (IBM Corp., Armonk, NY, USA). This study was approved by the Institutional Review Board of the Armed Forces Medical Command (Seongnam, Gyeonggi, South Korea).

3. Results

3.1. Identification of narcolepsy cases

Through DMSIS, 218 cases of narcolepsy and its related conditions were identified in Korean soldiers from January 2007 to December 2013. Of these, the medical records of 216 cases were reviewed and excluded two duplicate cases registered to different hospitals (Fig. 1). A total of 41 cases met the Brighton Collaboration case definition of narcolepsy: level 1, two cases (4.9% of 41 cases); level 2, 17 cases (41.0%); and level 3, 22 cases (53.7%). The other 175 cases, which corresponded to the diagnostic certainty level 4–5, were excluded from this study (level 4a, 40 cases; level 4b, 71 cases; and level 5, 64 cases). In DMSIS, the 41 eligible