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Vaccines and the risk of acute disseminated encephalomyelitis

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ABSTRACT

Background: It is important to examine the risk of Acute disseminated encephalomyelitis (ADEM) after vaccination.
Methods: We conducted a nested case–control study between January 2011 and December 2015. Four controls per case were matched for age, gender, address. An independent expert committee validated the diagnoses of cases and controls. Data on vaccinations were obtained from computerized vaccination records. The analyses were conducted with the use of conditional logistic regression.
Results: The analyses include 272 cases of ADEM and 1096 controls. No increase in the risk of ADEM was observed for vaccination against hepatitis B, influenza, polio(live), diphtheria, pertuss(acellular), tetanusis, measles, mumps, rubella, Japanese Encephalitis, meningitis, hepatitis A, varicella and rabies vaccines. Vaccine was associated with a statistically significant increase in risk in the 31–60-day exposure interval (OR, 4.04 [95% CI, 1.07–12.69]), but not the 0–30 and 61–180-day interval. There was no association between vaccine received and the recurrence of ADEM.
Conclusions: Findings from the present study do not demonstrate an association of vaccines with an increased risk of ADEM and its recurrence among either paediatric (≤18 years) or adult (>18 years) individuals within the 180 days after vaccinations. The finding in children in the 31–60 day risk interval is likely coincidental and was not confirmed in separate self-control analyses.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated central nervous system disorder, characterized by an acute encephalopathy with polyfocal neurological deficits [1]. The pathogenesis of ADEM is not known clearly, but adhesion molecules, chemokines, matrix metalloproteinase, and other cell factors are thought to be important in its occurrence and development [2].

In addition to a known association with infections, vaccinations also have been suggested to induce a small increased risk of ADEM [3]. In an American study, vaccination was found to precede ADEM in about 5% (2/42) of cases [4]. Several cases of young females presenting with onset of ADEM approximately 1 month following the administration of human papillomavirus (HPV) vaccine have been reported [5,6]. In Langer-Gould et al, a higher risk of CNS demyelinating disease was only observed in those less than 50 years at first 14 and 30 days, but not further longer period, following any vaccination (a "temporal shift" phenomenon) [7].

In recent years, the Expanded Program on Immunization (EPI) has been carried out in China. The type and number of vaccines administered to residents increased. The probability of having a severe abnormal reaction such as ADEM to vaccines is small, but the onset of such reactions usually cause widespread public concern. This may reduce public confidence in vaccines [8]. Vaccines available for use in Jiangsu Province was presented in Supplementary material Table 1.

The purpose of this study was to examine in more detail the association between the risk of ADEM including disease recurrence and vaccines.

2. Materials and methods

2.1. Setting

In China, most people get medical technology and specialized neurological care from public hospitals. Generally, patients who

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get suspected ADEM are admitted in hospital as emergencies, and soon after, a neurologist will be invited to take care of them. Patients no more than 16 years old who are affected by neurological diseases are usually taken in pediatric hospitals.

The province of Jiangsu is located in the east of China. It covers a surface of 107.2 thousand km^2 and the mean population density is 767 inhabitants/km^2. Nantong, Yancheng and Xuzhou, which are three cities in Jiangsu province, were involved in this study. Totally, 74 hospitals were involved, 21 in Nantong, 20 in Yancheng and 33 in Xuzhou, and they all provided inpatient services. In these hospitals, any departments that might have received patients meeting the case definition were involved, including neurology, internal medicine, pediatrics, and inpatient wards. The research was approved by the institutional review board of the Jiangsu Provincial Center for Disease Control and Prevention (JSCDC). Informed consent was waived because this was a medical records review study without direct patient contact.

2.2. Case identification

We searched the Hospital Information Systems (HIS) for first mention of International Classification of Diseases, Tenth Revision (ICD-10), diagnostic codes (G04.001, G04.002, G04.051, G04.903, and G04.912) for ADEM from January 1, 2011, to December 31, 2015, for persons of any age.

Diagnoses were confirmed by neurologists from clinical data, such as clinical manifestations, computed tomography (CT), electroencephalograph (EEG), cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) examinations. The consensus definitions of ADEM that were updated by the International Pediatric MS Study Group in 2013 were used [9]. The emergence of either new or old neurologic symptoms lasting more than 24 h, which stabilized or resolved either partially or completely, or lesions on MRI was defined as a relapse if it occurred >3 months after disease onset, and as a flare if it occurred ≤3 months after disease onset [10].

2.3. Control selection

For each ADEM case, 4 control individuals randomly selected from the same hospital with no history of ADEM were matched to the case according to year of birth (within 1 year), gender, and zip code (a surrogate measure for socioeconomic status) during the same period. The control participants were assigned the same index date as their matched case (symptom onset date). Controls were patients referred for headache (except trigeminal neuralgia), migraine, vascular or other diseases which were thought not to modify the probability of vaccination. Patients with chronic severe neurological diseases or autoimmune diseases were excluded.

2.4. Vaccination records

Information on vaccinations was obtained from Information Management System for Immunization Programming, in which anyone who received vaccinations would be registered, matched with ID number and verified by paper vaccination records. Any vaccination was considered to be an exposure. We collected information on all vaccinations received within 180 days.

2.5. Covariates

Other data obtained included nationality (Han and others), occupation, marital status (married and single), allergy, familial diseases, comorbid chronic diseases, and history of infectious diseases. Comorbid chronic diseases and history of infectious diseases were within 6 months before the index date.

2.6. Statistical analysis

Conditional logistic regression following univariable analysis was used to estimate the matched odds ratio (OR) and its corresponding 95% two-sided CI for the association between ADEM and vaccination. For each case, the index date was the date of onset of the first symptoms of the CNS demyelinating event. For the controls, we assigned the time of the onset of ADEM in the individual with whom the control was matched. The models were adjusted for nationality, occupation, marital status, allergy, familial diseases, comorbid chronic diseases, and history of infectious diseases within 6 months before the index date, and all variables with a P value less than 0.20 were included in the regression model [11]. To examine both the immediate and long-term effects of vaccination on ADEM, the exposure was restricted to the following different time frames before the index date: 14 days, 30 days, 60 days, 90 days, and 180 days. Additional analyses were stratified by subintervals 0–14, 15–30, 31–60, 61–90, and 91–180 days. To determine whether the paediatric was associated with any vaccine-associated ADEM, the study population was stratified according to age (≤18 years and >18 years) at the index date.

To examine whether or not each case was vaccinated in the 31–60 interval or the remainder of the 1 to 180 post-vaccination time interval, self-controlled case series (SCCS) analyses were used. To avoid the confounding by infection, we looked at cases without a history of infection in the prior 6 months separately. The risk interval was the 31–60 day interval and the comparisons interval included the remainder of the 1 to 180 post-vaccination time interval. We do the analysis for receipt of any vaccine and as many specific vaccines as possible. We also conducted separate analyses for children and adults.

The means (SDs) of normally distributed variables were compared using 2-sample t tests; for binary or categorical variables, χ^2 analysis with the Fisher exact test was used. We defined a P value less than 0.05 as statistically significant. All analyses were conducted in 2017.

3. Results

Totally, 272 patients with newly diagnosed ADEM were included in the study after an independent diagnosis of two neurologists (Fig. 1). A summary of selected characteristics of the cases (272) with ADEM and the controls (1096) is presented in Table 1.

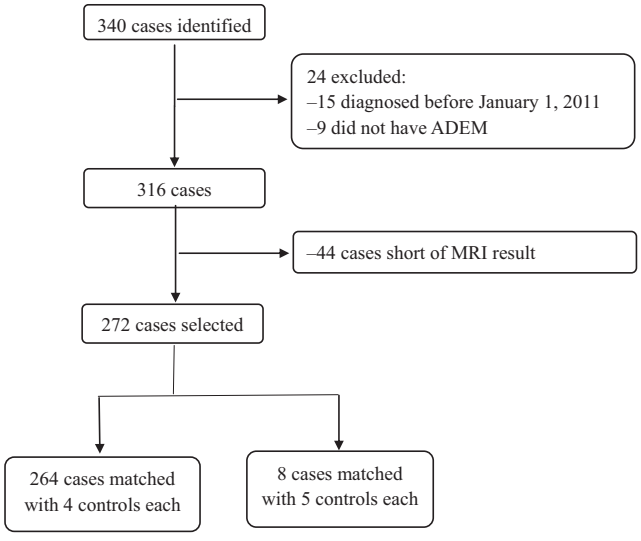

Fig. 1. Case classification flow.