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Allergy in patients with anti-*N*-methyl-D-aspartate receptor encephalitis

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ABSTRACT

Background and objective: Allergy is a potential outcome of dysregulated immune system. Previous studies have shown the association of allergy and autoimmune diseases, however, there is few study to investigate the relationship between allergy and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Thus, we investigate the rate of allergy in patients with anti-NMDAR encephalitis and analyze the risk factors.
Method: The rate of allergy was investigated in patients with anti-NMDAR encephalitis and was compared with patients with virus encephalitis. The clinical cutaneous characters were described in details. All patients with anti-NMDAR encephalitis were divided into allergic and nonallergic group. Clinical factors were compared in the two groups, and logistic regression model was also used to analyze possible risk factors of allergy.
Results: Patients with anti-NMDAR encephalitis had a higher rate of allergy than those with viral encephalitis (22.1% vs 9.2%, odds ratio (OR) = 3.23, confidence interval (CI) = 1.40–7.42, P = 0.006). In patients with anti-NMDAR encephalitis, allergic patients exhibited longer days in hospital (30 days vs 22 days, P = 0.005) and higher occurrence of decreased consciousness (81.5% vs 58.9%, P = 0.031), higher rate of complications (77.8% vs 57.9%, P = 0.046) and abnormal electroencephalography (EEG) (100% vs 78.6%, P = 0.021) than patients without allergy. Cerebrospinal fluid (CSF) antibody titers of allergic patients during the disease course were also higher than nonallergic patients (P = 0.004). However, further logistic regression analysis did not reveal independent predictors of allergy.
Conclusions: Patients with anti-NMDAR encephalitis show higher allergic rate than those with virus encephalitis. Patients with allergy show higher CSF antibody titers and greater illness severity. However, the final outcome of anti-NMDAR encephalitis was not influenced.

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a central nervous system (CNS) disease involving dysfunction of autoimmune system. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is associated with Immunoglobulin G (IgG) antibodies directed against the NMDAR1 (NR1) subunit of the NMDA receptor [1], which is more common in young women and sometimes accompanied with ovarian teratoma, presenting with psychiatric symptoms, seizure, cognition impairment, memory loss, consciousness disturbance, dyskinesia, autonomic instability, and hypoventilation [2,3].

Allergy and autoimmunity are two potential outcomes as a product of dysregulated immune system. There was an investigation presumed that allergy could be inversely related to autoimmune disease but this association is weak [4]. Some studies, however, reported that more than one autoimmune disorder was positively associated with physician-diagnosed common allergic disorders or a history of allergy to medications, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), autoimmune thyroiditis, multiple sclerosis, and type I diabetes mellitus [5–9]. While anti-NMDAR encephalitis belongs to the autoimmune disorders, few studies have focused on exploring its relationship with allergy. In the clinical practice, nevertheless, we indeed have found quite a few patients with anti-NMDAR encephalitis who had experienced allergic reaction during their hospitalization or came with past history of allergy. This study aimed to describe the incidence rate, clinical features, and the treatment of allergic reactions in patients with anti-NMDAR encephalitis. The clinical features during the course of anti-NMDAR encephalitis of both allergic and nonallergic groups were compared to analyze the relevant factors of allergy.

2. Method

2.1. Patients

From May 2013 to October 2016, 122 patients (50 male, 72 female) diagnosed with anti-NMDAR encephalitis in West China Hospital were

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included in this study. All patients presented CNS symptoms and anti-NMDAR body was detected in their CSF. Their diagnosis was confirmed to anti-NMDAR encephalitis diagnosis criteria [10].Clinical information was obtained by the authors or referring physicians during hospitalization period including the record of clinical manifestation and daily pathography as well as the results of electroencephalography (EEG), brain magnetic resonance imaging (MRI), CSF examinations, and laboratory findings. Abnormal EEG involves focal or diffuse slow activity, epileptic activity, extreme delta brush, and beta activity. Abnormal MRI results were mainly T1-weighted image (T1), T2-weighted image (T2), or Fliud Attenuated Inversion Recovery (FLAIR) signal hyperintensity in cortex, focal brain parenchyma swelling, white matter changes, and cortical atrophy. Abnormal CSF involves increased pleocytosis (>5/mm^3) or/and protein concentrations (>0.45 g/L).

On the other hand, from April 2015 to October 2016, 130 patients diagnosed with viral encephalitis (58 male, 72 female) who presented with the similar symptoms but their autoimmune antibody test was negative were included as the control group (bacteria, mycobacterium tuberculosis, fungus, parasite, rickettsia, spirochete, and prion were excluded). The serum and CSF samples of each patient were obtained simultaneously and then transferred to Peking Union Medical College Hospital in China for the detection of anti-NMDAR IgG antibody. All specimens (serum and CSF) were evaluated by indirect immunofluorescence using EU 90 cells transfected with the NMDAR1 subunit (NR1) of the NMDAR complex and immobilized on BIOCHIPs (Euroimmun AG, L €ubeck, Germany) as previously described [11]. After samples were incubated with transfected or untransfected cell lines, slides were washed and stained with fluorescein-labeled antihuman IgG antibodies and then visualized by a fluorescence microscope. The dilution starting point is 1:10 for serum and 1:1 (undiluted) for CSF. Samples were classified as positive or negative based on the intensity of surface immunofluorescence of transfected cells compared with nontransfected cells. Antibody titers in CSF and serum were described as negative, weak positive (CSF 1:1, serum 1:10), positive (CSF 1:10 or 1:32, serum 1:32), and strong positive (CSF 1:100 or 1:320, serum 1:100).

The diagnosis of allergy was based on the past medical history, the skin signs presented during the hospitalization period recognized and diagnosed by at least two dermatologists, and the reactions to antiallergic treatment. Existence of allergen, antiallergic treatment, and laboratory findings were recorded by the physicians. Mini-Mental State Examination (MMSE) was used to assess the cognitive symptoms [12]. The prognosis evaluation was made according to the modified Rankin Scale (mRS) at 4 weeks and every 3 months after the initiation of immunotherapy, and mRS score in the final follow-up was considered as outcome [13]. The outcome of patients with full recovery (mRS 0) or mild deficit (mRS 1–2) was considered to be 'good'; and the outcome of patients with severe deficit (mRS 3–5) or death (mRS 6) was considered to be 'poor'.

This study was approved by the local ethics committee of West China Hospital, Sichuan University. All subjects provided written informed consent for their participation.

2.2. Statistical analyses

The Statistic Package for Social Science (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) was used for evaluating statistical analyses. Univariate analyses were performed using the Mantel–Haenszel test for allergy and chi-squared test or Fisher's exact test for categorical variables like gender, symptoms, and examined results. Wilcoxon rank sum test was used for continuous variables such as age and length of hospital stay and ordered categorical data such as outcome. Kruskal–Wallis test was used to explore the relationship between allergy and antibody titer in CSF and serum. Predictors of allergy were estimated using a logistic regression model. Hazard ratios (HRs) in the cox model and corresponding 95% confidence interval (CI) were conducted to evaluate the strength of association. $P < 0.05$ (two-sided) was considered as significant.

3. Results

A total of 122 patients with definitive diagnosis of anti-NMDAR encephalitis were enrolled in this study, including 50 male (41.0%) and 72 female (59%) patients with a median age of 25.5 years (range 9–71), among which 27 (22.1%) patients suffered from allergic reactions during disease course or had allergic history. In the control group, however, there were only 12 out of 130 (9.2%) patients who experienced allergic reactions (58 males (44.6%), 72 females (55.4%), age: 8–82 years, median 34.5 years). The age distribution between two groups is significantly different between two groups ($P < 0.000$) and there is no difference in gender ($P = 0.560$). After adjusting significant difference of age between the two groups, patients with anti-NMDAR encephalitis had a higher incidence of allergy compared with that in the control group (22.1% vs 9.2%, OR = 3.23, CI = 1.40–7.42, $P = 0.006$).

3.1. Clinical manifestations of allergy

In the 27 allergic patients with anti-NMDAR encephalitis, the median age was 20 years, ranging from 9 to 71 years, with 19 (70.4%) female and 8 (29.6%) male patients. All of them had allergic history (n = 9, 33.3%) or experienced the allergic reaction during the disease course (n = 18, 66.7%). As for those who suffered allergy after admission, the median length of hospital stay was 39 days (range 22–106), and the allergic reaction mostly occurred on the 19th day (range 2th–49th days), while the patients were under or after immunotherapy. Allergic symptoms were primarily mild or moderate cutaneous signs such as local or extensive flushing and pruritus, urticaria pigmentosa, and palpable maculopapular rash. Skin lesions were given a percentage of total body surface area according to the technique employed to assess burns; 22.2% patients (n = 6) were above 70%, 7.4% patients (n = 2) were in 40–70%, 25.9% patients (n = 7) were 40% or less, and 44% patients (n = 12) were out of record. The abnormal results of laboratory examination involved mild liver damage (n = 2), eosinophilia (n = 1), and electrolyte disturbances (n = 3). Severe allergic reactions such as allergic shock, Steven–Johnson syndrome, and epidermal necrolysis syndrome were not found in all patients according to their symptoms and laboratory examinations.

The identified allergens in patients with anti-NMDAR encephalitis are pollen (n = 1), some proteins (n = 1), ammonium chloride (n = 1), quetiapine (n = 1), antiepileptic drugs (n = 5) like oxcarbazepine, levetiracetam, carbamazepine, and antibiotics (n = 4) such as sulfonamides. The rest of patients (n = 14) who were reported with allergic reactions, their underlying causes of allergy were unknown.

In 18 patients with cutaneous signs during their hospitalization time, if certain, allergens have been avoided during the therapeutic process and the antiallergic therapy was started. Loratadine (n = 18) and glucocorticoid (n = 7) were the primary therapeutic drug, glycyrrhizin (n = 5), ketotifen fumarate (n = 4), calcium (n = 11), and Vitamin C (n = 5) were used as auxiliary treatments. In addition, intravenous immunoglobulin and methylprednisolone for anti-NMDAR encephalitis also have strong therapeutic effect on allergy. All allergic cutaneous symptoms did not get worse which lasted 2–14 days and subsided after antiallergic therapy.

3.2. The difference of clinical features between allergic and nonallergic groups with anti-NMDAR encephalitis

The comparison between allergic group and nonallergic group of patients with anti-NMDAR encephalitis about clinical features is shown in Table 1. The hospitalization period was longer in neurology ward for the allergic group compared with the nonallergic group (30 days, range from 17 to 118 days vs 22 days, range from 8 to 113 days, $P = 0.005$).

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