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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.

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, $P = 0.005$).

Table 1
Comparison of clinical features between allergic group and nonallergic group with anti-NMDAR encephalitis.

	In total n(%)	Allergy n(%)	Nonallergy n(%)	P value
Number	122	27	95	–
Gender				
Male	50(41.0%)	8(29.6%)	42(44.2%)	0.174
Female	72(59.0%)	19(70.4%)	53(55.8%)	
Median age, range (years)	9–71/23	9–71, 20	11–57, 26	0.246
Median length of hospital stay, range (days)	17–118, 24	17–118, 30	1–113, 22	0.002
Prodromal symptoms	67(54.9%)	17(63.0%)	50(52.6%)	0.341
Initial symptoms				
Psychiatric	72(59.0%)	17(63.0%)	55(58.0%)	0.575
Seizure	35(28.7%)	8(29.6%)	28(29.5%)	
Other*	15(12.3%)	2(7.4%)	12(12.6%)	
Psychiatric symptoms	116(95.1%)	26(96.3%)	90(95.0%)	1
Speech disturbances	35/99(35.4%)	8/21(38.1%)	27/78(34.6%)	0.767
Seizure	103(84.4%)	25(92.6%)	78(82.1%)	0.239
GTCS*	80(77.7%)	19(76.0%)	61(78.2%)	–
CPS*	21(20.4%)	6(24.0%)	15(15.8%)	
SE*	45(43.7%)	10(40.0%)	35(44.9%)	
Dyskinesias and movement disorders	49(40.1%)	12/15(80.0%)	37/58(63.8%)	0.607
Cognition	77/88(87.5%)	13/15(86.7%)	64/73(87.7%)	1
Decreased consciousness	63.(40%)	22(81.4%)	56(58.9%)	0.031
Autonomic instability	76(62.3%)	9(33.3%)	25(26.3%)	0.473
Complications	62.(30%)	21(77.8%)	55(57.9%)	0.046
Tumor*	21(17.2%)	6(22.2%)	15(15.8%)	0.563
Tumor resection	16(13.1%)	5/6(83.3%)	11/15(73.3%)	–
Mechanical ventilation	30(24.6%)	8(30.0%)	22(23.2%)	0.491
Tracheotomy	18(14.8%)	3(11.1%)	15(15.8%)	0.545
ICU	16(13.1%)	2(7.4%)	14(14.7%)	0.319

*Other initial symptoms in nonallergy group involving headache and fever, numbness and weakness in limbs, lalopathy, memory decline, unresponsive, dyssomnia and fever, involuntary movement, blurred vision, in allergic group involving numbness of tongue tip and left thumb, lalopathy, and numbness in limbs. *GTCS: generalized tonic–clonic seizures; *CPS: complex partial seizure; *SE: status epilepticus; *Tumor: in allergic patients: teratoma; in nonallergic patients: teratoma, teratoma concomitant with choriocarcinoma, hamartoma of kidney, hypophysoma, renal carcinoma, adrenal adenoma, carcinoma of urinary bladder, human choriocarcinoma with teratoma, and pulmonary metastasis.

Allergic patients were more likely to exhibit decreased consciousness than patients in the nonallergic group (81.5% vs 58.9%, P = 0.031). Complications occurred more frequently in allergic groups than in nonallergic group (77.8% vs 57.9%, P = 0.046), including pulmonary infection (n = 66.7% vs 49.5%), urinary system infection (25.9% vs 16.8%), liver dysfunctions (7.4% vs 13.7%), electrolyte disturbance (11.1% vs 9.5%), alimentary tract hemorrhage (11.1% vs 5.3%), hypoproteinemia (11.1% vs 5.3%), and Hashimoto's thyroiditis (3.7% vs 0%).

Table 2
Comparison of ancillary examinations between allergic group and nonallergic group with anti-NMDAR encephalitis.

Ancillary examination	In total n(%)	Allergy n(%)	Nonallergy n(%)	P value
Abnormal MRI* findings	48/117(41.0%)	9/25(36.0%)	39/92(42.4%)	0.565
Abnormal EEG* findings	88/106(83.0%)	22/22(100%)	66/84(78.6%)	0.021
Abnormal CSF* findings*	82(67.2%)	20(74.1%)	62(65.3%)	0.389

*MRI: magnetic resonance imaging; *EEG: electroencephalogram; *CSF: cerebrospinal fluid.
*Abnormal CSF findings are irrelevant to anti-NMDAR antibody and just involve increased pleocytosis (>5/mm^3) or/and protein concentrations (>0.45 g/L).

Positive antibody in CSF was detected in all patients with anti-NMDAR encephalitis and serum was detected in 72 (59.0%) patients. The antibody titers in CSF of allergic group were tended to be higher than the nonallergic group (P = 0.05), and it is also higher in those patients who had experienced allergy during their disease course compared with others who had only allergic history (P = 0.004) (Fig. 1). There is no trend about antibody tires in serum between the two groups.

Abnormal EEG was found more frequently in the allergic group than in the nonallergy group (100% vs 78.6%, P = 0.021, Table 2). It showed diffusing slow wave activities in 9 cases (40.9%), epileptiform discharges in 4 cases (18.2%), extreme delta brush in 7 cases (31.8%), and diffusing beta activities in 2 cases (9.1%). The rates of abnormal MRI and CSF were not significantly different between the two groups (P > 0.05, Table 2).

In all patients, the common immune therapies were intravenous immunoglobulin (55, 45.1%), methylprednisolone (7, 5.7%), or both (55, 45.1%). The median follow-up duration was 14 months (range 5–37 months), 88 patients (84.6%) had a good outcome (mRS 0–2), and 16 patients (15.4%, morality: 10.6%) had a poor outcome (mRS 3–6) with 18 patients out of touch. No significant difference in treatment or prognosis existed between the two groups (P > 0.05, Table 3).

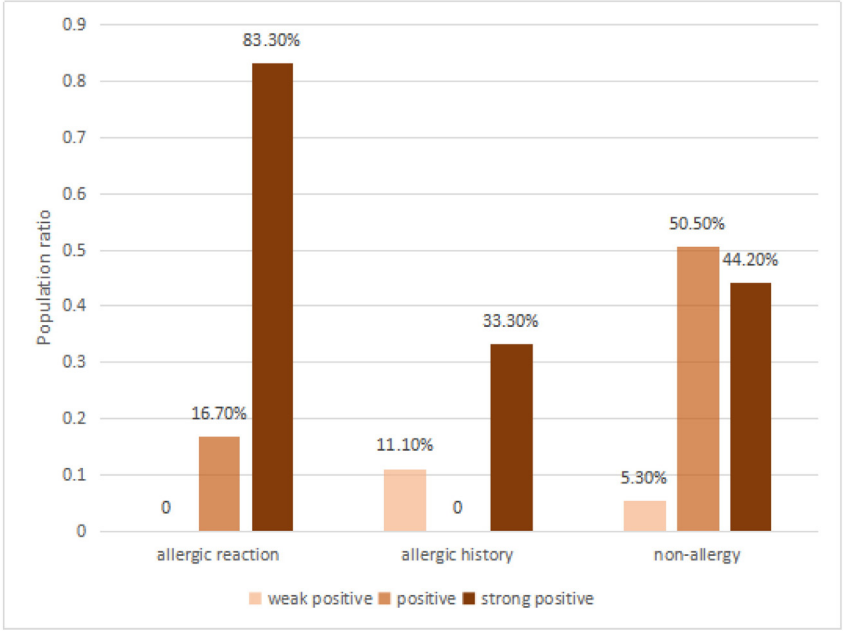

Fig. 1. Antibody titer in CSF*. *Compare between three groups, P value = 0.004. Graphics program: Microsoft Office Word.

Table 3
Comparison of prognosis between allergic group and nonallergic group with anti-NMDAR encephalitis.

	Allergy n(%)	Nonallergy n(%)	P value
Prognosis	24/27	80/95	0.518
mRS 0–2	19(79.2%)	69(86.2%)	
mRS 3–6	5(20.8%)	11(13.8%)	
Morality	2/24(8.3%)	9/80(11.3%)	1

3.3. Multivariable analysis of predictors of allergy

The multivariable analysis results did not show any significant association between allergy and any factors like hospital stay, sex, age, decreased consciousness, seizure, and antibody titer in CSF ($P > 0.05$, Table 4).

4. Discussion

In this study, we found that allergy is common in patients with anti-NMDAR encephalitis. Approximately 22% patients had history of allergy or presented allergy during the acute process. The main symptom of allergy is cutaneous lesion such as local or extensive flushing and pruritus, urticaria pigmentosa, and palpable maculopapular rash. It reveals the coexistence of allergy with autoimmune diseases again in one individual.

Interestingly, though 18 patients suffered allergic reactions, there is no serious allergy such as allergic shock, Steven–Johnson syndrome, and epidermal necrolysis syndrome in patients with NMDAR encephalitis. The reason is not clear. It may be attributed to the immune therapies for patients with anti-NMDAR encephalitis. Firstly, as the first line drug for anti-NMDAR encephalitis, intravenous immunoglobulin and methylprednisolone are also useful for allergy. Secondly, patients presented allergy during the acute illness process, which could be covered by immune therapy treatment just in time. Third, the rate of allergy may be higher than that in the present if there is no immune therapy for patients.

In this study, we found that a higher CSF antibody titer in patients with allergy than those without allergy, especially in those who suffered from allergy during acute disease process. As allergic patients also stayed longer in hospital, with higher rate of decreased consciousness and complications and abnormal EEG than nonallergic patients, we speculate that patients with allergy are more likely to present serious condition. The higher antibody tires in CSF cause more serious dysfunction of CNS neurons, which leads to decreased consciousness, longer stay in hospital, more complications, and abnormal EEG. The patients with allergy have higher NMDAR antibody titer and allergy is more likely to be activated in serious condition, which indicates that allergy may be considered as a clinical marker of illness severity. Therefore, to people with allergy, more attention should be paid to prevent serious illness in acute process. It also indicates that hypoallergenic antiepileptic drugs and antibiotics should be considered firstly in patients with anti-NMDAR encephalitis. During hospitalization, we should consciously observe abnormal skin performance and other clinical manifestations of allergy for earlier diagnosis and treatment. Besides, carefully inquiring of allergic history, performing skin test before using antibiotic, and avoiding common allergens are needed.

Though allergy may be considered as a marker of illness severity, it did not influence the final outcome of anti-NMDAR encephalitis. The present study did not show the difference of final outcome between patients with allergy and nonallergy. It indicates that allergy just be involved in acute process of anti-NMDAR encephalitis. It may be caused by activated inflammation pathway. Unfortunately, the present retrospective study could not provide with the relative evidence.

However, some evidences about the coexistence mechanism of allergy and autoimmune disease may provide some clues. In patients with multiple sclerosis, Interleukin-17 (IL-17) that produced by T helper (Th) 17 cells promotes B cell class to produce immunoglobulin E (IgE) antibodies, which may conduct to allergy [14,15]. The Interleukin-4 (IL-4) as one of T helper (Th) 2 cytokines that play important roles in allergy can also be found in RA, a prototypical T helper (Th) 1-skewed disease [16]. In autoimmune thyroiditis, a T-suppresser cell defect predisposes to both thyroiditis and atopic syndrome [17]. The above evidences of association between allergy and other autoimmune disease may provide clues and basis for further study.

The present study has some limitations: first, retrospective study may cause some bias in the study. Second, not all allergens were identified in allergic reactions. Third, there were no laboratory data about allergen-specific IgE or IgG, Phadiatop test, and skin prick test.

Table 4
Multivariate analysis of factors associated with allergy in patients with anti-NMDAR encephalitis.

Variables	OR	95% CI*	P value
Sex	1.985	0.745–5.294	0.171
Age	0.988	0.947–1.031	0.577
Decreased consciousness	2.141	0.511–8.981	0.298
Complications	1.394	0.340–5.724	0.645
Antibody tires in CSF*			0.173
Antibody tires in CSF(1)*	0.758	0.076–7.567	0.814
Antibody tires in CSF(2)*	0.395	0.149–1.045	0.061

*CI, confidence interval; *Antibody tires in CSF: weak positive; *Antibody tires in CSF(1): positive; *Antibody tires in CSF(2): strong positive.

5. Conclusion

Allergy is a common symptom of anti-NMDAR encephalitis. Patients with allergy also show higher CSF antibody titer, longer hospital stay and higher rate of decreased consciousness, complications and abnormal EEG than patients without allergy. However, allergy does not influence the respond to immunotherapy or the prognosis.

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Disclosure of conflict of interest

No financial or other potential conflicts of interest exist.

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