Antibody prevalence and immunotherapy response in Chinese patients with epilepsy and encephalopathy scores for patients with different neuronal surface antibodies

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Abstract

Background: The scale assessment was helpful in predicting the presence of antibodies to autoimmune encephalitis. This study aimed to evaluate the application of antibody prevalence in Chinese patients with epilepsy and encephalopathy (APE2-CHN) and response to immunotherapy in Chinese patients with epilepsy and encephalopathy (RITE2-CHN) for patients with different neuronal surface antibodies.

Methods: A total of 1365 patients with epileptic seizures as the prominent feature in Xuanwu Hospital, Capital Medical University, from June 2016 to June 2020 were enrolled in our study. Of these, 915 patients with epilepsy of unknown etiology whose serum and/or cerebrospinal fluid samples were examined for autoimmune antibodies were selected. All patients were scored with antibody prevalence in patients with epilepsy and encephalopathy (APE2), response to immunotherapy with epilepsy and encephalopathy (RITE2), APE2-CHN, and RITE2-CHN scores.

Results: Of the 915 patients, 191 patients were positive for neural-surface specific antibodies (115 N-methyl-D-aspartate receptor (NMDAR) Ab, 47 leucine-rich glioma-inactivated protein 1 (LGI1) Ab, 8 contactin-associated protein 2 (CASPR2) Ab, 4 AMPA2R-Ab, and 11 GABAR-B-Ab; 3 CASPR2-Ab and LGI1-Ab, 2 NMDAR-Ab and CASPR2-Ab, and 1 NMDAR-Ab and myelin-oligodendrocyte glycoprotein [MOG] Ab). The sensitivity and specificity of APE2 ≥ 4 in predicting the presence of neural-surface specific antibodies in our study were 74.35% and 81.77%, respectively, and the sensitivity and specificity of APE2-CHN ≥ 4 were 75.92% and 84.53%, respectively. Eight cases had an APE2 score < 4 and APE2-CHN score ≥ 5; all these patients had memory decline as the prominent manifestation. We divided the patients into six groups according to the different antibodies. APE2-CHN scores showed higher sensitivity for the prediction of NMDAR-Ab, but lower sensitivity for LGI1-Ab. A total of 187/191 (97.91%) patients received immunotherapy and 142/191 (74.35%) patients benefited from the treatments. The patients who were positive for LGI1-Ab with RITE2-CHN ≥ 8 responded well to immunotherapy.

Conclusions: APE2-CHN had the highest value for predicting the positivity of NMDAR-Ab and RITE2-CHN evaluated the response of immunotherapy for anti-LGI1 encephalitis appropriately. However, RITE2 and RITE2-CHN do not appear to be good predictors of immunotherapy outcomes for patients with specific neuronal-surface antibodies and high APE2-CHN scores are often indicative of a poor response to immunotherapy.

Keywords: APE2-CHN; RITE2-CHN; APE2; RITE2; Neuronal surface antibody; Immunotherapy

Introduction

In the last few decades, with a rapidly increasing pace of discovery of specific neurological autoantibodies (Abs), the relationship between immune origin and autoimmune encephalopathy or epilepsy has received plenty of attention.¹,² In 2017, The International League Against Epilepsy (ILAE) officially classified immune etiology as one of the six etiological groups of epilepsy (structural, genetic, infectious, metabolic, and immune, in addition to an unknown group).³ Previous studies have found that more than 10% of epileptic patients had an underlying autoimmune origin.⁴ A study conducted by Dubey et al.⁵ reported that 34.8% patients with epilepsy of unknown etiology were positive for immunological neuronal antibodies. The discovery of specific neuronal antibodies

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provides a new evidence for the immunotherapy to patients with drug-refractory epilepsy.

Early diagnosis of autoimmune encephalopathy or epilepsy and application of immunotherapy can contribute to a significant clinical improvement. Therefore, Dubey et al.[4] designed an antibody prevalence in epilepsy (APE) score based on clinical, imaging, and laboratory data to estimate the probability of positivity prior to antibody test results for patients with epilepsy or encephalopathy. Then, the APE scores were modified in three aspects, including brain magnetic resonance imaging (MRI) criteria, tumor history diagnosis, and score for faciobrachial dystonic seizure (FBDS). The antibody prevalence in patients with epilepsy or encephalopathy (APE2) score improved the predictive value of autoimmune epilepsy or encephalopathy.[6] Subsequently, based on APE2 score, Liu et al.[7] added three variables of clinical data to the scoring system and created a new score named antibody prevalence in Chinese patients with epilepsy and encephalopathy (APE2-CHN) score in 2020, which may increase the predictive rate of the presence of neuronal antibodies. Additionally, response to immunotherapy with epilepsy and encephalopathy (RITE2) and response to immunotherapy in Chinese patients with epilepsy and encephalopathy (RITE2-CHN) scores were calculated for patients who received immunotherapy, which had been proved to be useful to predict the prognosis of patients with epilepsy or encephalitis with unknown etiology.[6,7]

Both APE2 and APE2-CHN scores were useful tools in predicting positive neuronal Abs findings. However, the above two studies were not performed according to different types of antibodies. Thus, we collected 191 patients with epilepsy or encephalopathy positive for neuronal surface antibodies to assess the antibody prediction rates of APE2 and APE2-CHN scores and evaluated whether the predictive value of the two scores is related to the different types of antibodies.

Methods

Ethical approval

The study was approved by the Institutional Research Ethics Committee of Xuanwu Hospital (No. 2017YFC0907702) and written informed consent was obtained from each subject.

Patients

A total of 1365 patients with epileptic seizures as the prominent feature in Xuanwu Hospital, Capital Medical University, from June 2016 to June 2020 were enrolled in our study. The patients with underlying metabolic abnormalities or presence of structural brain lesions that would explain their seizures were excluded. Among them, 915 patients with epilepsy of unknown etiology whose serum and/or cerebrospinal fluid (CSF) samples were examined for autoimmune antibodies were selected. Of these, 191 patients were positive for neuronal surface antibodies including 185 patients with one antibody (115 had NMDAR-Ab, 47 had leucine-rich glioma-inactivated protein 1 (LGII1) Ab, 8 had contactin-associated protein 2 (CASPR2) Ab, four had AMPA2R-Ab, and 11 had GABAR-B-Ab) and six with >1 antibody (three had CASPR2-Ab and LGI1-Ab, two had NMDAR-Ab and CASPR2-Ab, and one had NMDAR-Ab and MOG-Ab). A total of 21 patients who were positive for non-specific neuronal antibodies (four had Hu-Ab, two had Yo-Ab, and 15 had glutamic acid decarboxylase 65 [GAD65] Ab) were excluded [Figure 1].

Antibody testing

We tested the serum and CSF samples from patients before immunotherapy for Abs targeting NMDAR, AMPA1/2-R, GABAA/B-R, LGI1, CASPR2, DPPX, IgLON5, MOG, GAD 65, Hu, Ri, Yo, amphiphysin, and CRMP5/CV2 by cell-based assay (EUROIMMU, FA112d-1, Germany).

Patient scale scores

All of 915 patients were scored with APE2, APE2-CHN, RITE2, and RITE2-CHN according to clinical manifestations, tumor history, CSF examination, brain MRI, and so on. Treatment effect was evaluated by the modified Rankin score (mRS) and responder was defined as ≥1 change in mRS at follow-up visit, whereas for the patients with epileptic seizure as the single symptom, responder was defined as >50% reduction of seizure frequency 6 months after immunotherapy.

Statistical analysis

All statistical analyses were performed with the SPSS version 19.0 (SPSS Inc, Chicago, IL, USA). Univariate analyses of nominal and interval variables were performed using the chi-square, McNemar or Fisher exact test, and Mann-Whitney test, respectively. A two-side P < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Of the 915 patients, 191 patients were positive for neuronal surface antibodies, 110 (57.59%) were male, and the age was 29.29 ± 15.12 (6–81) years. Two (1.05%) patients had a history of malignancy and others had no remarkable past history. Fifty-nine (30.89%) patients had prodromal symptom of cold, such as headache, sore throat, runny nose, or fever. Clinical presenting symptoms comprised of seizure onset (191 patients [100%]), including new-onset epilepsy (159 patients [83.25%]) and established epilepsy of unknown etiology (32 patients [16.75%]), psychological and behavioral abnormalities (115 patients [60.21%]), cognitive impairment (122 patients [63.87%]), speech disorder (50 patients [26.18%]), autonomic nervous disorder (32 patients [16.75%]), FBDS (6 patients [3.14%]), other movement disorders (37 patients [19.37%]), decreased level of consciousness (54 patients [28.27%]) and at least two types of antiepileptic drugs (AEDs) (56 patients [29.32%]).
APE2 and APE2-CHN scores

All of 915 patients were scored by APE2 and APE2-CHN scales. With a cutoff of 4, 274 patients (29.95%) had APE2 scores ≥4. Of the 191 patients with neuronal surface antibodies, 42 patients (74.35%) had APE2 scores ≥4. The sensitivity and specificity of APE2 ≥4 in predicting the presence of neural-surface specific antibodies in our study were 74.35% and 81.77%, respectively. In addition, with a cutoff of 5 score, 257 cases (28.09%) had APE2-CHN scores ≥5. Of the 191 patients with neuronal surface antibodies, 145 cases (75.92%) had APE2-CHN scores ≥5, and the sensitivity and specificity of APE2-CHN ≥4 were 75.92% and 84.53%, respectively. There were no statistical differences between APE2 and APE2-CHN in sensitivity and specificity for predicting neurological Abs positivity to autoimmune encephalitis or epilepsy (P > 0.050).

For demographic variables of 191 patients, the age of patients in groups of APE2 ≥4 or APE2-CHN ≥5 was higher than those in groups of lower scores [Table 1]. Although antibody predictive rates were similar for both scores, eight cases had APE2 scores <4 and APE2-CHN scores ≥5 [Table 2]. By summarizing the clinical data of these eight patients [Supplementary Table 1, http://links.lww.com/CM9/A723], all of the eight patients had memory decline as the prominent manifestation, five...
Table 1: Comparison of demographic variables of cases by APE2 and APE-CHN scores.

| Items             | APE2 scores | APE2-CHN scores |
|-------------------|-------------|-----------------|
|                   | ≥4 (n = 142) | <4 (n = 49)     | P     | ≥5 (n = 145) | <5 (n = 46) | P     |
| Age (years)       | 32 (7.81)   | 52 (6.76)       | 0.001 | 32 (7.81)   | 47.5 (6.76) | 0.011 |
| Male              | 84 (59.15)  | 26 (40.85)      | 0.457 | 87 (60.00)  | 23 (50.00)  | 0.232 |

Data are presented as median (range) or n (%). Results of Mann-Whitney test or Pearson chi-squared test comparing the APE ≥4/APE < 4 and APE-CHN ≥3/APE-CHN < 3 of patients targeting neural-surface Abs, respectively. Abs: Autoantibodies; APE2: Antibody prevalence in patients with epilepsy and encephalopathy; APE2-CHN: antibody prevalence in Chinese patients with epilepsy and encephalopathy.

Table 2: APE2 and APE2-CHN scores in 191 patients with neural-surface antibodies.

| APE2/APE2-CHN | APE2 ≥4 | APE2-CHN ≥5 | APE2-CHN <5 | Total |
|---------------|---------|-------------|-------------|-------|
| APE2 ≥4       | 137     | 5           | 41          | 142   |
| APE2 <4       | 8       | 46 (24.08)  | 49 (25.65)  | 99    |

APE2: Antibody prevalence in patients with epilepsy and encephalopathy; APE2-CHN: antibody prevalence in Chinese patients with epilepsy and encephalopathy.

Table 3: Comparison of patients with different Abs by APE2 and APE-CHN scores (n = 191).

| Abs      | NMDA (n = 115) | GABA-B (n = 11) | LGI1 (n = 47) | CASPR2 (n = 8) | AMPA (n = 4) | Two antibodies (n = 6) | P    |
|----------|----------------|-----------------|---------------|----------------|--------------|------------------------|------|
| APE2 ≥4  | 99 (86.09)     | 8 (72.73)       | 26 (55.32)    | 4 (50.00)      | 3 (75.00)    | 2 (33.33)              | <0.001|
| APE2-CHN ≥5 | 101 (87.83) | 8 (72.73)       | 25 (53.19)    | 4 (50.00)      | 4 (100.00)   | 3 (50.00)              | <0.001|

Data are presented as n (%). Results of Pearson chi-squared test. Abs: Antibodies; APE2: Antibody prevalence in patients with epilepsy and encephalopathy; APE-CHN: Antibody prevalence in Chinese patients with epilepsy and encephalopathy.

Patients developed speech disorders, and four patients suffered from severe consciousness decline. According to these three clinical features, a total of 122 patients had cognitive impairment, 91 patients (74.59%) had APE2 scores ≥4, and 99 patients (81.15%) had APE2-CHN scores ≥5 (P = 0.280). Fifty cases developed speech disorders in the course of disease, 37 cases had APE2 scores ≥4 (74%), 42 cases (84%) had APE2-CHN scores ≥5 (P = 0.326). Fifty-four cases presented as decreased level of consciousness, 50 cases (92.59%) had APE2 scores ≥4, and 54 cases (100%) had APE2-CHN scores ≥5 (P = 0.126). In addition, all three symptoms were present in 12 patients, 11 patients (91.67%) had APE2 scores ≥4, and all patients had APE2-CHN scores ≥5 (P = 1.000).

As shown in Table 3, we divided the patients into six groups according to the different types of antibodies, and each patient was assigned with the APE2 and APE2-CHN scores, respectively [Figure 2]. Among them, 86.09% (99/115) patients with NMDAR-Ab had APE2 ≥4, while only 50% (4/8) patients with LGI1-Ab had APE2 ≥4 (χ² = 17.922, P < 0.001). Moreover, 87.83% (101/115) patients with NMDAR-Ab had APE2-CHN ≥5, while only 53.19% patients with LGI1-Ab had APE2-CHN ≥5 (χ² = 23.156, P < 0.001). Compared with the predictive value for LGI1-Ab, both APE2 and APE2-CHN scores had a higher value for prediction of NMDAR-Ab. By comparison between different groups, APE2 and APE2-CHN scores showed highest sensitivity of predicting the presence of NMDAR-Ab, but low sensitivity for LGI1-Ab.

**Treatment schedule and effect**

Glucocorticoids, intravenous immunoglobulin (IVIG), and plasma exchange were classified as first-line immunotherapy for autoimmune encephalitis and immunosuppressants as second-line immunotherapy. Of the 191 patients, 187 (97.91%) received immunotherapy, including 126 patients (67.38%), 52 patients (27.81%), and nine patients (4.81%) with one type, two types, and three types of first-line immunotherapy, respectively. Eighteen patients (9.63%) received immunosuppressive drug as second-line therapy for disease. The remaining four patients did not receive immunotherapy because of patient decision. A total of 142 (74.35%) benefited from the immunotherapy and 49 (25.65%) had poor effect. The therapeutic efficiency of different types of antibodies is shown in Table 4.

**RITE2 and RITE2-CHN**

Both RITE2 and RITE2-CHN scores were performed on all patients for predicting immunotherapy response. With a cutoff of 6 score, 168 patients (87.96%) had a RITE scores ≥6 and 72.02% of them responded well to immunotherapy. In addition, with a cutoff of 8 score, 151 patients (79.06%) had a RITE2-CHN scores ≥8 and 70.68% of them benefited from the treatments. There was no statistical difference between the two scores in predicting the response to immunotherapy (P > 0.050). Then, further analysis was carried out according to the
different types of antibodies as shown in Table 5. With RITE2 score ≥6, 86.11% (31/36) patients with LGI1-Ab, 70.37% (76/108) patients with NMDAR-Ab, 80% (4/5) patients with CASPR2-Ab, 54.55% (6/11) patients with GABA-Ab, and 50% (2/4) patients with amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)
Table 5: Comparison of patients with different antibodies by RITE2 and RITE2-CHN scores (n = 191).

| Antibodies               | Items                              | NMDA (n = 115) | GABA-B (n = 11) | LG1 (n = 47) | CASPR2 (n = 8) | AMPA (n = 4) | Two Abs (n = 6) | P   |
|--------------------------|------------------------------------|----------------|----------------|--------------|---------------|--------------|----------------|------|
| RITE2 and treatment effect | RITE ≥6, response to treatment,    | 76/108 (70.37) | 6/11 (54.55)   | 31/36 (86.11) | 4/5           | 2/4          | 2/4            | 0.114|
|                          | RITE <6, response to treatment,    | 6/7 (85.71)    | 0              | 10/11 (90.91) | 3/3           | 0            | 2/2            | 1.000|
| RITE2-CHN and treatment effect | RITE-CHN ≥8, response to treatment | 71/101 (70.30) | 6/11 (54.55)   | 24/28 (85.71) | 2/3           | 2/4          | 2/4            | 0.174|
|                          | RITE-CHN <8, response to treatment | 11/14 (78.57)  | 0              | 17/19 (89.47) | 5/5           | 0            | 2/2            | 0.784|

Data are presented as n/N or n/N (%). Results of Pearson chi-squared test or Fisher exact test. Abs: Antibodies; RITE2: response to immunotherapy with epilepsy and encephalopathy; RITE2-CHN: Response to immunotherapy in Chinese patients with epilepsy and encephalopathy.

Ab benefited from immunotherapy. Although there was no statistical difference between different groups (P = 0.114), the patients positive for LGI1-Ab had a highest rate of improvement after immunotherapy. By that analogy, with RITE2-CHN score ≥8, 85.71% (24/28) patients responded well to immunotherapy. The results revealed that either RITE2 or RITE2-CHN score had the highest value to predicting immunotherapy response for anti-LGI1 encephalitis after treatments.

Discussion

In this study, we evaluated the application of APE2 and APE2-CHN scores for patients with neuronal surface antibodies. Of the 915 patients with epilepsy of unknown etiology whose serum and/or CSF samples were examined for autoimmune antibodies, the APE2 scores (sensitivity: 74.35%, specificity: 81.77%) and APE2-CHN scores (sensitivity: 75.92%, specificity: 84.53%) were valuable equally to identify patients with the highest probability of harboring neurological Abs. APE2-CHN score, which was based on APE2 score, increased three terms of the clinical performance, including cognitive disorders, speech impairment, and decreased level of consciousness, to evaluate the clinical characteristics more comprehensively. The above three clinical manifestations are not uncommon in patients with autoimmune encephalitis.[4] Therefore, we analyzed the clinical data of 191 patients with these three clinical features; APE2-CHN ≥5 had a higher sensitivity in predicting the presence of neuronal surface antibodies for patients with the above three clinical features.

Then we analyzed the clinical data of 191 patients positive for neuronal surface antibodies and divided the patients into six groups according to the difference of antibodies. We found that either APE2 or APE2-CHN score had the highest predictive rates of anti-NMDAR encephalitis. Anti-NMDAR encephalitis, discovered in 2007,[9] was the most common autoimmune encephalitis with a broad clinical spectrum of symptoms,[8,9] and APE2 or APE2-CHN score based on clinical, imaging, and laboratory data, which led to the highest score of APE2 or APE2-

CHN scores for patients with anti-NMDAR encephalitis. On the contrary, our study indicated that the predictive rate of CASPR2-Ab was the lowest. Except for epileptic seizure, anti-CASPR2 encephalitis was often presented with severe peripheral nerve damage causing Morvan syndrome,[10,11] which may reduce the sensitivity and specificity of APE2 or APE2-CHN to predict the presence of CASPR2-Ab.

Subsequently, we summarized the treatment and prognosis of 191 patients, and 74.34% patients responded well to immunotherapy. For autoimmune encephalitis, glucocorticoids, IVIG, and plasmapheresis were used as the first-line treatment, and immunosuppressive agents were used as the second-line treatment.[10,12] To judge the application time of immunotherapy accurately, Dubey et al.[6] designed RITE2 score for predicting the response of treatment, and then Liu et al.[7] drew up a new evaluation on RITE2-CHN score. In this study, the two scores showed similar value of predicting the response to immunotherapy and both scores had the highest predictive rate for anti-LGI1 encephalitis for improvement after treatment. By comparing the two groups of responders and non-responders, we found that abnormal mental behavior, dystonia, and decreased level of consciousness were prominent in non-responders group and APE2 score of non-responders group was higher than responders group, which was not consistent with the findings of previous research by Dubey et al.[6] For those patients positive for specific neuronal surface antibodies, the complicated clinical symptoms led to the increase of APE2 or APE2-CHN score, which also led to the exacerbation of clinical conditions, resulting in the difficulty of treatment. Similarly, patients with a RITE2 or RITE2-CHN score within the cutoff of scores had better outcomes than those with a RITE2 or RITE2-CHN score above the cutoff. When patients were positive for neuronal surface antibodies, RITE2 or RITE2-CHN scores seem not to be a good indicator of immunotherapy effectiveness. The scores were not capable of assessing the severity of clinical symptoms and immunotherapy may be ineffective in the presence of a single severe symptom.

There are some limitations in our study. Our study aimed to evaluate the application of APE2-CHN and RITE2-
CHN scores for patients with different specific neuronal surface antibodies, the patients with no-specific neuronal antibodies, such as Hu, Yo, and GAD-65 antibodies were not included. Additionally, the number of patients in six groups with different antibodies was not matched and the number of patients with NMDAR-Ab was 115, whereas the number of patients with AMPAR was only 4, which was far less than patients with NMDAR-Ab; that might reduce the accuracy of the results in statistical analysis.

Conclusions

APE2-CHN and RITE2-CHN scores are both useful screening tools in predicting positive neuronal surface antibody of immunological etiology and evaluating the response of immunotherapy in patients of epilepsy or encephalopathy. Both APE2 and APE2-CHN had the highest predictive value in the presence of NMDAR-Ab and RITE2 and RITE2-CHN have the highest value in evaluating the response of immunotherapy for anti-LGI1 encephalitis. In clinical practice, APE2-CHN score is more recommended for patients with speech disorders as the prominent symptom. Neither RITE2 nor RITE2-CHN appear to be good predictors of immunotherapy outcomes for patients with specific neuronal surface antibodies and high APE2 scores may often be indicative of a poor response to immunotherapy.

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Conflicts of interest

None.

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