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Clinical features of antibody-negative autoimmune encephalitis: A meta-analysis and literature review

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Abstract

Objective: This study aimed to conduct a comprehensive literature review and meta-analysis of antibody-negative Autoimmune encephalitis (AE) and to quantitatively compare the clinical features of antibody-negative versus antibody-positive AE patients. *Methods:* Systematic searches of the PubMed, Embase, Web of Science, and Chinese databases (China National Knowledge Infrastructure, Wanfang, and VIP) were conducted up to December 2023. Relevant articles including references and similar documents from retrieved papers, were further screened. Standardized mean differences (SMD) or odds ratios (OR) with 95% confidence intervals (CI) were calculated using fixed-effect or random-effect models for demographic characteristics, clinical manifestations, magnetic resonance imaging (MRI) and electroencephalogram (EEG) abnormalities, and cerebrospinal fluid (CSF) parameters. Subgroup analyses were performed to identify sources of heterogeneity. *Results:* Six studies (one prospective and five retrospective case-control studies) detailing the clinical features of antibody-negative AE were included in the meta-analysis. Compared to patients with antibody-positive AE, those with antibody-negative AE had a significantly older age at onset (SMD = 0.26, 95% CI: 0.04, 0.49; P = 0.02), a lower incidence of concurrent tumors (OR = 0.57, 95% CI: 0.31, 1.07; P = 0.08), and a lower CSF pleocytosis rate (OR = 0.46, 95% CI: 0.27, 0.79; P = 0.01). No significant differences were observed in sex distribution, clinical manifestations, MRI or EEG abnormality rates, or CSF protein concentrations. Furthermore, subgroup analysis demonstrated a lower prevalence of epileptic seizures among Western populations with antibody-negative AE compared to their Asian counterparts (P = 0.03).
Conclusion: This meta-analysis revealed significant differences in age of onset, tumor comorbidity, and CSF pleocytosis rate between patients with antibody-negative and antibody-positive AE, contributing to a more nuanced understanding of antibody-negative AE among clinicians.

Keywords: Autoimmune encephalitis; antibody-negative; clinical features; seronegative

INTRODUCTION

Autoimmune encephalitis (AE) encompasses a spectrum of central nervous system inflammatory disorders driven by autoimmune reactions.[1] Clinically, AE manifests with acute or subacute onset of behavioral and cognitive deficits, seizures, psychiatric symptoms and altered consciousness.[2] Based on the presence or absence of specific autoantibodies in serum and cerebrospinal fluid (CSF), AE is classified into antibody-positive and antibody-negative subtypes.[3] The pathogenesis of antibody-positive AE has been extensively elucidated and is primarily attributed to autoantibodies targeting neuronal surface or intracellular antigens. These antibodies may induce neurological dysfunction through various mechanisms, including receptor antagonism, cytoskeletal perturbation, or neuronal apoptosis.[4,5] Conversely, the etiology of antibody-negative AE remains poorly understood and may be associated with unrecognized antibodies or aberrant cellular immune responses.[3,6]

Epidemiological studies estimate that the annual incidence of AE is 0.8 cases per 100,000 people, with a prevalence of 13.7 cases per 100,000 people, exhibiting an upward trend year-on-year.[7] Within this patient population, antibody-negative AE constitutes a substantial proportion,

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with prevalence estimates ranging from 27.8% to 50.7% of all AE cases.[8-13] Despite the considerable frequency of antibody-negative AE, comparative studies of the clinical features distinguishing antibody-negative from antibody-positive AE patients are relatively limited. Consequently, a deeper exploration of the clinical features of antibody-negative AE is imperative to advance our understanding of this condition and to inform diagnostic and therapeutic approaches.

The present study aimed to conduct a systematic literature review and meta-analysis of published research on antibody-negative AE patients, adhering to predefined inclusion and exclusion criteria. Our primary objective was to systematically evaluate the clinical features of patients with antibody-negative AE, thereby providing novel insights to enhance diagnostic accuracy and treatment strategies, while also establishing a foundation for future research endeavors.

METHODS

Literature search

This study adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. The study protocol was pre-registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY), registration number INPLASY202440093. A comprehensive electronic literature search was performed in multiple databases, including PubMed, Embase, Web of Science, and Chinese databases (China National Knowledge Infrastructure, Wanfang, and VIP). The search strategy employed a combination of MeSH terms with free-text keywords, specifically: ("autoimmune encephalitis"[MeSH] OR "autoimmune encephalitis"[tiab]) AND ("seronegative"[tiab] OR "antibody negative"[tiab]). The search encompassed all published literature up to December 31, 2023. To ensure comprehensive coverage, reference lists of retrieved articles and related literature were manually scrutinized. Following the removal of duplicate entries, two independent researchers performed a preliminary screening of titles and abstracts for potential inclusion. Any discrepancies in selection were resolved through consensus-based discussion among the research team.

Inclusion and eExclusion Criteria

The eligibility criteria for the included studies were as follows: (1) Study design: Prospective or retrospective case-control study. (2) Participants: Patients diagnosed with an antibody-negative AE based on the diagnostic criteria by Graus *et al*.[3] (3) Control Group: Patients with antibody-positive AE. (4) Outcomes: Demographic characteristics, clinical presentations, cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) findings, and cerebrospinal fluid (CSF) parameters. (5) Languages: Studies published in English and Chinese. Exclusion criteria: Case reports, review articles, commentaries, conference abstracts, and non-case-control studies were excluded. Furthermore, studies with duplicate publications, animal or in vitro studies, and research specifically addressing pediatric autoimmune encephalitis were also excluded.

Data extraction

The following data were extracted from the included studies: basic study information (first author, year of publication, study location), study design, sample size, demographic characteristics of participants, clinical presentations, rates of cranial MRI abnormalities, electroencephalogram abnormalities, and CSF parameters. The data were collated and organized using Microsoft Excel.

Quality assessment

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for case-control studies.[14] This scale evaluates three domains: selection (4 points), comparability (2 points), and exposure (3 points), with a maximum score of 9. Studies scoring 5 or above were deemed moderate-quality or high-quality and were included in the meta-analysis. Two reviewers independently performed the quality assessment, and any disagreements in scoring were resolved through discussion.

Statistical analysis

Statistical analyses were conducted using R software version 4.3.0 with the 'metafor' package and executed on the SPSSAU platform developed in R (https://spssau.com/) to ensure the accuracy and reproducibility of the analyses. Dichotomous variables were analyzed using odds ratio (OR) and 95% confidence interval (CI) to aggregate effect sizes, while continuous variables were assessed using the standardized mean difference (SMD) and 95% CI. Heterogeneity among studies

was evaluated using Cochran's Q test and the I^2 statistic. A fixed-effects model was applied when the Q test P value was >0.1 and I^2 was <50%; a random-effects model was used when the P value was ≤0.1 or I^2 was ≥50%. Publication bias was assessed using Egger's linear regression test and Begg's rank correlation test, with a P value >0.05 indicating no significant publication bias. Sensitivity analyses were performed by sequentially excluding studies to assess the impact of individual studies on the overall effect size.

RESULTS

Study characteristics

A systematic literature search identified 30 articles, of which 6 met the inclusion criteria and were included in the meta-analysis (Table 1). These studies included a total of 354 patients, with 164 in the antibody-negative group and 190 in the antibody-positive group. The sample sizes of the included studies ranged from 18 to 150 participants. All were case-control studies, consisting of one prospective study and five retrospective studies. All studies achieved scores above 5 on the NOS, reflecting moderate to high quality. The process of study selection for the meta-analysis is illustrated in Figure 1.

We analyzed antibody detection methods across the included studies. Five studies (Berger *et al*, Probasco *et al*, Baumgartner *et al*. and Li *et al*)[8-10,12-13] conducted tests on both serum and CSF, while Pradhan et al primarily used CSF,

Table 1: Demographic and clinical features of patients with autoimmune encephalitis: Comparing antibody-negative and antibody-positive groups

First author, year	Country	sample size	Study Design	Female (%)	Mean Age, year	Concurrent tumor*	Psychiatric symptom*
Berger, 2023[8]	Germany	150 (74/76)	Retrospective	47/57	50/48.9	14/21	58/50
Probasco, 2017[9]	America	61 (29/32)	Retrospective	55/53	57/39	7/13	24/47
Li, 2019[10]	China	38 (16/22)	Retrospective	44/45	46/38	13/14	69/73
Pradhan, 2019[11]	India	31 (15/16)	Prospective	20/38	NA/NA	7/13	47/56
Baumgartner, 2013[12]	Germany	18 (5/13)	Retrospective	60/54	61/53	20/23	NA/NA
Guo, 2019[13]	China	56 (25/31)	Retrospective	56/52	44/39.5	8/19	56/71

Table 1. Continued. (%)

First author	Seizures*	Memory deficits*	Altered* consciousness	Abnormal MRI*	Abnormal EEG*	CSF Pleocytosis*	CSF protein elevation*
Berger, 2023	35/54	76/75	22/24	80/74	60/54	28/39	56/56
Probasco, 2017	31/50	72/78	86/69	NA/NA	NA/NA	NA/NA	NA/NA
Li, 2019	81/45	25/55	13/41	63/33	73/85	25/64	31/14
Pradhan, 2019	47/56	40/44	NA/NA	53/50	87/81	NA/NA	NA/NA
Baumgartner, 2013	NA/NA	NA/NA	80/27	75/58	80/60	NA/NA	NA/NA
Guo, 2019	80/71	28/48	28/32	40/52	76/81	44/65	24/16

* Indicates percentages. Abbreviations: Nos = Newcastle-Ottawa Scale

resorting to serum only when lumbar puncture was declined (11/31 patients). Four studies (Berger *et al*, Pradhan *et al*, Baumgartner *et al*, and Guo *et al*)[8,11-13] explicitly described using immunoblot techniques, but none mentioned tissue-based indirect immunofluorescence testing or live cell-based assays. Probasco *et al*. and Li *et al*. did not detail their testing methods.[9,11]

Meta-analysis results

Age at onset

All six studies reported the mean age at onset for both antibody-negative AE patients and antibody-positive AE patients (Figure 2). There was no significant heterogeneity among the studies (Q = 4.48, P = 0.345, I^2 = 10.74%); thus, a fixed-effects model was applied for analysis. The results indicated that the mean age at onset was significantly greater in the antibody-negative group than in the antibody-positive group (SMD = 0.26, 95% CI: 0.04, 0.49; P = 0.02).

Tumor comorbidities

Tumor comorbidities were assessed during hospitalization or follow-up in six studies (Figure 3). There was no significant heterogeneity among the studies (Q=0.612, P=0.987, I^2=0.00%). The incidence of tumors was significantly lower in the antibody-negative group than in the antibody-positive group (OR = 0.58, 95% CI: 0.43, 0.77; P = 0.08).

Notably, Berger *et al*. conducted fluoro-deoxyglucose positron emission tomography (FDG-PET) scans in the majority of their cohort (84.7%, 127/150). Similarly, Baumgartner *et al*. and Probasco *et al*. performed FDG-PET examinations on all study participants to screen for malignancies in autoimmune encephalitis patients. Li *et al*. employed a multi-modal approach, with

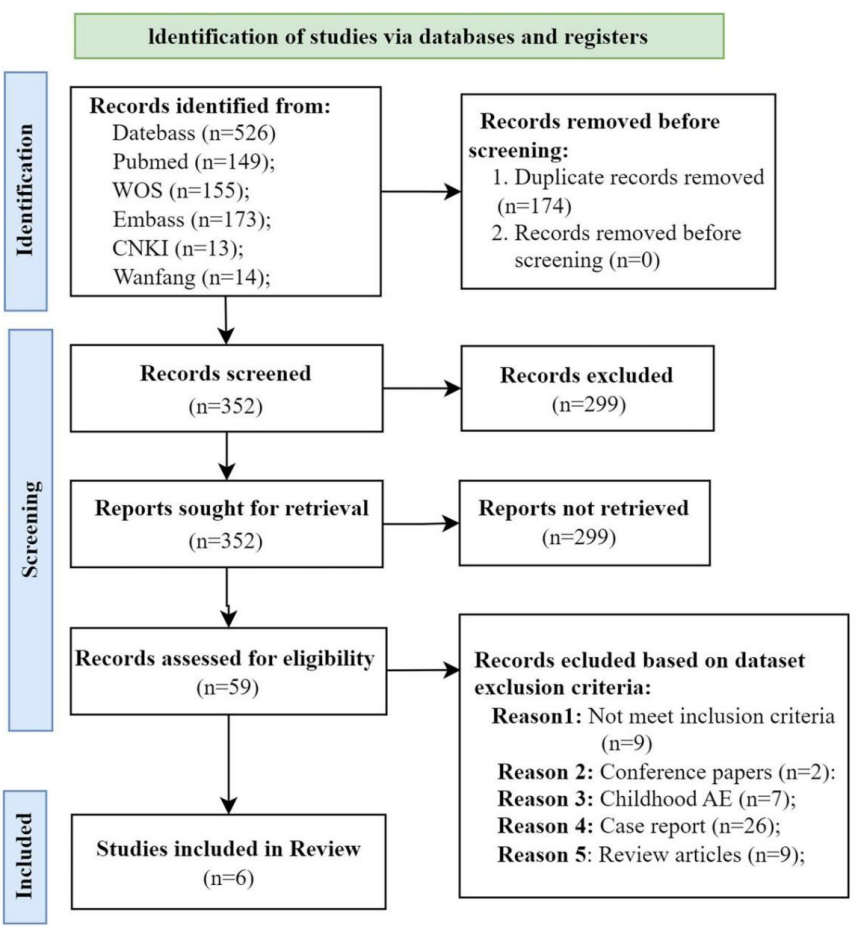

Figure 1. Flow diagram of the study selection process for the meta-analysis.

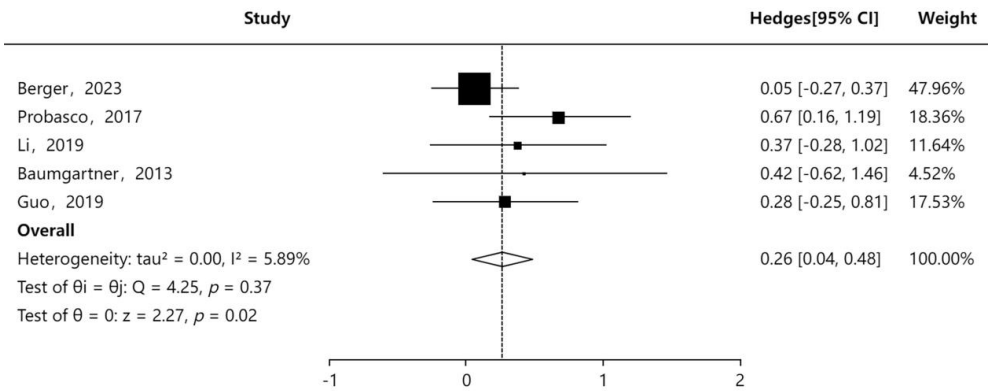

Figure 2. Forest plots comparing age between patients with antibody-negative AE and patients with antibody-positive AE

73.7% (28/38) of patients undergoing tumor marker tests and abdominal and gynecological ultrasonography, while 86.8% (33/38) received chest computed tomography scans for further tumor screening. However, Guo *et al*. did not specify their tumor screening methodology.

CSF parameters

Three studies examined CSF pleocytosis rates among patients and demonstrated no significant heterogeneity (Q = 1.97, P = 0.37, I^2 = 0.00%). The meta-analysis revealed a significantly lower incidence of CSF pleocytosis in the antibody-negative group than in the antibody-positive group (OR = 0.46, 95% CI: 0.27, 0.79; P = 0.01; Figure 4).

Other demographic and clinical characteristics

We analyzed potential differences between antibody-negative AE and antibody-positive AE patients in terms of sex distribution, clinical manifestations (such as seizures, memory impairments, psychiatric symptoms, and altered consciousness), and ancillary test results (cranial MRI abnormality rate, EEG abnormality rate, and elevated CSF protein levels). The meta-analysis revealed no statistically significant differences between the groups for these variables.

Specifically, the sex distribution (OR = 0.84, 95% CI: 0.55, 1.28, P = 0.41) suggested similar male-to-female ratio in both groups. There were no significant differences in the proportions of patients who experienced epileptic seizures (OR = 0.91, 95% CI: 0.40, 2.06; P = 0.82), psychiatric symptoms (OR = 0.84, 95% CI: 0.54, 1.29; P = 0.34), memory impairments (OR = 0.69, 95% CI: 0.43, 1.10; P=0.14), or decreased levels of consciousness (OR = 1.11, 95% CI: 0.25, 4.97; P = 0.85).

Similarly, the groups were no comparable in terms of ancillary test abnormalities, such as the

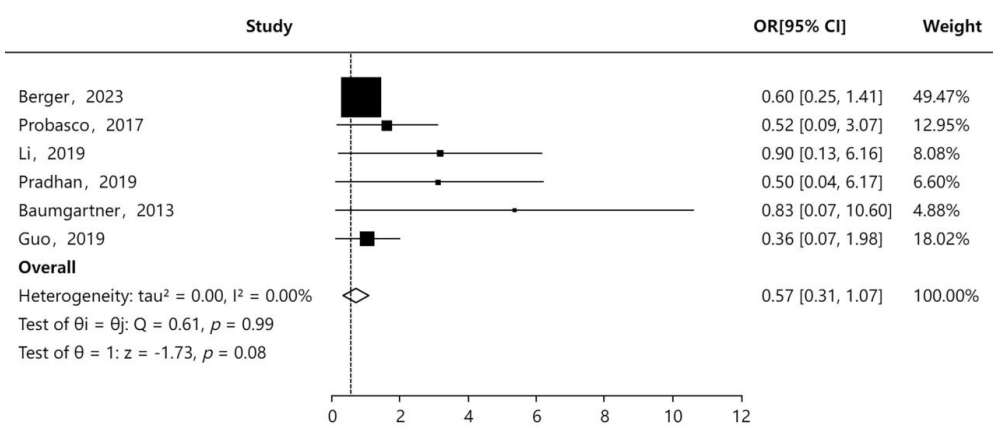

Figure 3. Forest plots comparing concurrent tumor status between patients with antibody-negative AE and patients with antibody-positive AE

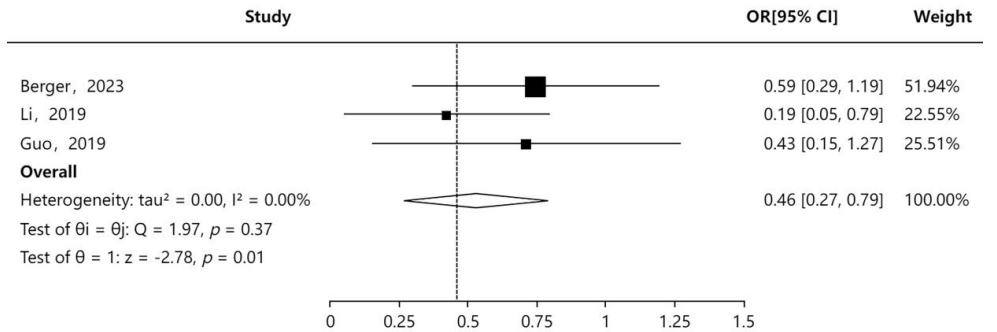

Figure 4. Forest plots comparing CSF pleocytosis between patients with antibody-negative AE and patients with antibody-positive AE

proportion of patients with elevated CSF protein levels (OR = 1.21, 95% CI: 0.70, 2.10; P = 0.85), cranial MRI abnormality rate (OR = 1.31, 95% CI: 0.78, 2.18; P = 0.32), and EEG abnormality rate (OR = 1.13, 95% CI: 0.66, 1.94; P = 0.66).

However, significant heterogeneity was observed in the incidence of epileptic seizures across studies (Q = 10.80, P = 0.03, I^2 = 62.96%). Subgroup analysis based on ethnic and regional characteristics, divided into Western and Asian groups, revealed a lower incidence of epileptic seizures in Western populations with antibody-negative AE compared to their Asian counterparts (P = 0.03) (Figure 5).

Publication bias assessment and sensitivity analysis

We assessed publication bias for the 11 included indices using Egger's linear regression test and Begg's rank correlation test. Most indices showed no apparent publication bias. However, potential risks were indicated for indices related to epileptic seizures (Egger's test P = 0.149; Begg's test P = 0.050).

Sensitivity analysis, conducted by sequentially excluding individual studies, demonstrated minor fluctuations in effect size estimates without substantively altering the main conclusions. The confidence intervals for the combined effect sizes

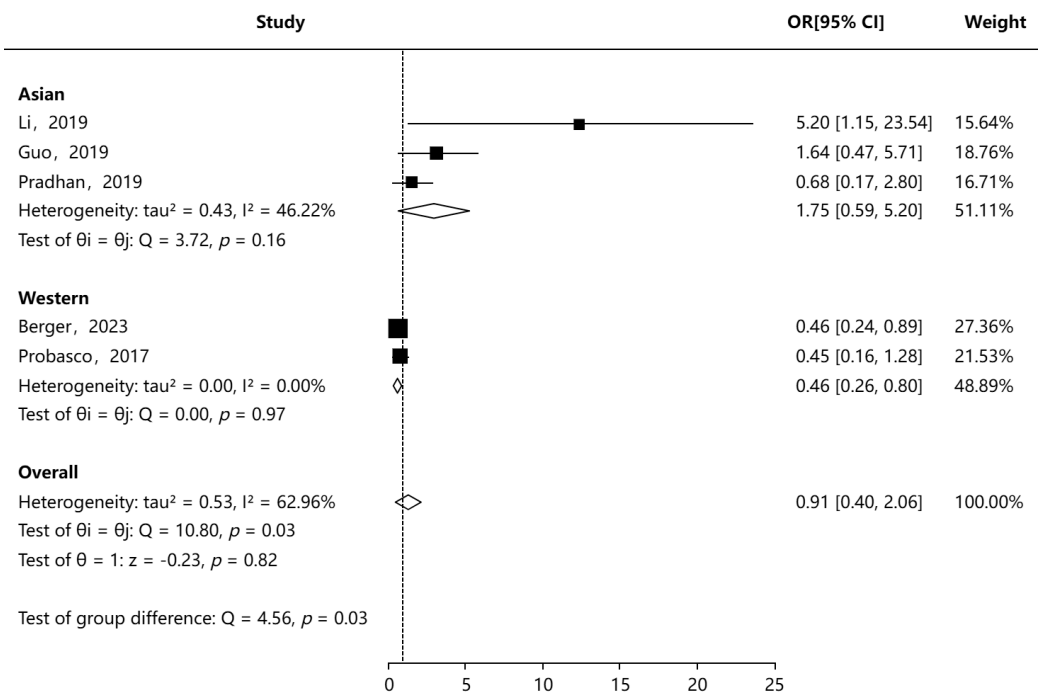

Figure 5. Forest plot comparing the occurrence of seizures between patients with antibody-negative AE with subgroup analysis based on population.

of all indices remained consistent, indicating high robustness of the study's conclusions regarding the selection of included studies.

DISCUSSION

Demographic and Oncological features

This meta-analysis revealed a significant difference in age of onset between antibody-negative and antibody-positive AE patients, with the combined effect analysis indicating a substantially higher mean age of onset in the antibody-negative group. This finding provides a novel perspective for exploring the potential pathophysiological mechanisms of antibody-negative AE and suggests a possible association with immunosenescence.

Several hypotheses have been proposed regarding the pathogenesis of antibody-negative AE, including autoantibody titers below detection thresholds, the presence of unidentified novel antibodies, and non-antibody-mediated cytotoxic T-cell responses.[3,15-16] Immunosenescence, an age-related degenerative change in immune function, may promote the development of antibody-negative AE through multiple mechanisms.[17] With advancing age, B-cell dysfunction may lead to a reduction in autoantibody levels below detection thresholds, resulting in an apparent antibody-negative state. Additionally, T-cell subset imbalances in elderly patients, characterized by a decrease in naive T cells and an increase in memory T cells, may promote T-cell-mediated autoimmune responses.[18] Age-related decline in regulatory T-cell function may result in loss of self-tolerance, potentially triggering autoimmune responses less dependent on antibody production.[19] The synergistic effects of these mechanisms may explain the higher age of onset observed in antibody-negative AE patients. However, given the complexity and heterogeneity of AE, further in-depth research is necessary to elucidate the precise pathophysiological mechanisms.

Tumor comorbidity is a significant clinical feature in patients with AE.[20] Our meta-analysis revealed a substantial difference in tumor prevalence between antibody-positive and antibody-negative AE patients. Compared to antibody-positive patients, those with antibody-negative AE exhibited a significantly lower incidence of concurrent tumors. Furthermore, we observed potential differences in tumor subtype distribution between the two groups. Several studies support these findings. Berger *et al*. conducted FDG-PET scans for malignancy screening in the majority of their cohort (84.7%, 127/150), revealing a significantly lower incidence of bronchial carcinoma in antibody-negative patients compared to antibody-positive patients (1.4% vs. 10.5%, P=0.034).[8] This trend was further corroborated by Baumgartner *et al*., who performed FDG-PET examinations on all patients and found that both cases of bronchial carcinoma were antibody-positive.[12] These findings suggest a potential association between antibody status and the occurrence of specific tumor types.

However, Probasco *et al*. provided a different perspective. In their study, FDG-PET scans were performed on all AE patients, revealing a significantly higher proportion of antibody-negative patients with a history of lymphoma compared to antibody-positive patients (17.2% vs. 0.00%, P=0.09).[9] These contrasting results suggest that patients with different antibody statuses may have varying susceptibilities to specific cancer types.

Beyond tumor comorbidities, significant differences in the prevalence of other immune-mediated diseases were observed between antibody-positive and antibody-negative AE patients. Li *et al*. revealed that antibody-positive AE patients more frequently presented with concurrent immune-related disorders, such as hypothyroidism, hyperthyroidism, rheumatoid arthritis, and type 1 diabetes (45.45% vs. 6.25%, P=0.012).[10] This finding suggests that antibody-positive AE patients may possess a specific type of autoimmune susceptibility, not only increasing their risk of autoimmune diseases in other organ systems but potentially promoting the occurrence of antibody-positive AE itself.[21,22] This particular immune dysregulation tends to generate antibody-mediated autoimmune responses, including antibodies targeting neuronal surface or synaptic proteins, as well as autoantibodies in other organ systems.

However, this differential distribution of immune-related diseases is not exclusive to antibody-positive AE patients. Conti *et al*. provided an interesting contrast in their study, demonstrating that antibody-negative autoimmune atrophic gastritis is more prevalent in elderly populations, and these patients exhibit a significantly lower incidence of autoimmune thyroiditis.[23] This observation underscores the complex interplay between antibody status, age, and autoimmune disease manifestations in different organ systems.

Clinical features

Our study comprehensively examined the differences in major clinical manifestations between antibody-negative and antibody-positive AE patients. The meta-analysis revealed no statistically significant differences between the two groups in the incidence of epileptic seizures, psychiatric symptoms, memory impairment, and altered consciousness. However, the occurrence of epileptic seizures demonstrated significant inter-group heterogeneity, prompting an in-depth subgroup analysis.

This subgroup analysis unveiled an intriguing geographical disparity: in Western populations, antibody-negative AE patients exhibited a lower incidence of epileptic seizures compared to antibody-positive patients, consistent with findings by Berger *et al*. and Probasco *et al*.[8,9] Conversely, studies by Li *et al*. and Guo *et al*. on Asian populations showed a higher seizure incidence in the antibody-negative group. This finding strongly suggests that the association between antibody status and epileptic seizures may be significantly influenced by ethnic background.[10,13]

This geographical variation likely stems from a complex interplay of factors, including genetic influences and differences in autoantibody distribution. Genetic variations may affect immune system function, neurological susceptibility, or autoantibody production, with potential differences in the expression patterns of epilepsy susceptibility genes across ethnicities. The uneven distribution of specific autoantibodies among different ethnic groups may lead to differences in the composition of antibody-positive and negative patient populations. However, no direct studies have yet explored whether these factors significantly impact the epilepsy incidence in antibody-negative AE patients across different ethnic backgrounds, although they may provide a potential theoretical basis for explaining the observed phenomena.

Regarding the diversity of clinical presentations, Titulaer *et al*. found that 87% of AE patients exhibited at least four clinical manifestations, while only 1% presented with a single clinical symptom.[24] This aligns with Li *et al*.'s findings for antibody-positive patients. However, Li *et al*.[10] also discovered that only 37.5% of the antibody-negative group presented with four or more clinical manifestations, significantly lower than the antibody-positive group (P=0.027). This finding suggests that antibody-negative patients may exhibit less diverse clinical presentations compared to their antibody-positive counterparts.

Examinations

Our study compared CSF, EEG, and MRI results between antibody-positive and antibody-negative AE patients, revealing significant differences in some aspects. CSF analysis showed that antibody-positive AE patients had a significantly higher proportion of increased CSF cell counts compared to antibody-negative patients. However, no significant difference was observed in CSF protein levels between the two groups. Notably, Berger *et al*. found that antibody-negative AE patients had a significantly higher proportion of elevated CSF albumin quotient compared to antibody-positive patients (43.1% vs. 26.8%, P=0.041).[8] The albumin quotient, an important indicator for assessing blood-brain barrier (BBB) function, suggests that antibody-negative AE patients may experience more severe BBB disruption.[25] Concurrently, they observed that antibody-negative AE patients had a significantly lower rate of oligoclonal band positivity compared to antibody-positive patients (17.1% vs. 30.9%, P=0.059)[8], potentially indicating reduced local immunoglobulin synthesis in the central nervous system (CNS) of antibody-negative AE patients.

These findings suggest that antibody-negative AE patients may experience more severe BBB disruption compared to antibody-positive patients, while the latter may exhibit more pronounced immune responses in the CNS. The BBB differences may stem from more severe primary BBB damage in antibody-negative AE patients, rather than secondary to inflammatory responses. As a protective barrier between blood and brain tissue, BBB damage may allow neurotoxic substances, immune cells, and potential pathogens to enter the CNS, triggering inflammatory and immune responses. Previous studies have confirmed that various autoimmune diseases (such as multiple sclerosis, systemic lupus erythematosus psychosis, and neuromyelitis optica) are closely associated with BBB damage leading to the entry of blood-borne toxic metabolites into the CNS, causing neuronal damage.[26-28] This mechanism may provide a new perspective on the pathogenesis of antibody-negative AE. In cases of severe BBB disruption, peripheral antibodies and immune cells may enter brain tissue through the damaged barrier, even in the absence of typical autoimmune encephalitis antibodies, leading to immune-mediated neuronal

injury. This mechanism could explain why some patients exhibit clinical symptoms and pathological changes similar to antibody-positive AE, despite the absence of known autoantibodies in their serum and CSF.

Regarding imaging and electrophysiological examinations, our study found no significant differences in MRI abnormality rates between the two groups. Previous studies investigating specific MRI manifestations, including limbic encephalitis, multifocal demyelination, inflammatory lesions, atrophic changes, and lesion enhancement, also found no significant differences.[8] EEG analysis showed no significant difference in overall abnormality rates between the groups. However, Berger *et al*.'s study suggested potential differences in the distribution of EEG abnormality types: diffuse slow wave activity was more common in antibody-negative AE patients (60.3% vs. 52.5%), while epileptiform discharges were relatively less frequent (5.9% vs. 9.8%).[8]

Treatment and prognosis

Although the exact pathogenic mechanism of antibody-negative AE remains incompletely elucidated, current treatment strategies largely mirror those for antibody-positive AE, given the potentially shared immunopathological basis. Standard first-line treatment protocols include high-dose corticosteroids, intravenous immunoglobulin, and plasma exchange.[29-31] For patients unresponsive to first-line therapies, second-line immunotherapies such as rituximab or cyclophosphamide may be considered. Previous study indicates that the time interval from disease onset to immunotherapy significantly influences prognosis.[29] However, the diagnostic uncertainty in antibody-negative AE may lead to treatment delays and insufficient intensity, potentially affecting therapeutic outcomes.[32]

Berger *et al*.'s study revealed significant differences in treatment approaches between antibody-negative and antibody-positive AE patients. A lower proportion of antibody-negative patients received immunotherapy compared to antibody-positive patients (74% vs. 87%, P=0.043). Although both groups showed similar response rates to immunotherapy, with comparable symptom improvement (79.2% vs. 73.7%, P=0.433), antibody-negative patients had longer hospital stays (34.8±36.4 vs. 47.6±52.3 days, P=0.090) and higher modified Rankin Scale (mRS) scores at discharge (2.6 vs 2.0, P<0.001).[8]

Regarding long-term prognosis, existing studies suggest that approximately half of antibody-negative AE patients ultimately achieve favorable outcomes. Lee *et al*.'s follow-up study of 147 antibody-negative AE patients found that 57% had good outcomes (mRS<3) after two years.[33] This aligns with Berger *et al*.'s observations, reporting that 46% of antibody-negative AE patients and 68% of antibody-positive AE patients achieved good outcomes (mRS 0-2) during the follow-up period.[8] Notably, variations in outcome assessments may partly stem from differing thresholds used to define "good outcome" based on mRS scores across studies.

Furthermore, previous studies has identified several factors associated with poor prognosis in antibody-negative AE patients. These include refractory status epilepticus, age of onset ≥60 years, acute necrotizing limbic encephalitis subtype, cerebellar atrophy, infratentorial lesions, and delayed immunotherapy exceeding one month.[33] These findings provide crucial reference points for identifying high-risk patients and implementing more aggressive interventions in clinical practice.

The primary limitation of this study is the paucity of research on the clinical characteristics of antibody-negative AE, resulting in a relatively small sample size for our meta-analysis. This constraint may have impacted our ability to draw more precise conclusions. Future research should focus on conducting larger-scale, more detailed subgroup analyses to further elucidate the clinical features of antibody-negative AE. Moreover, the development of novel high-sensitivity diagnostic tools and specific biomarkers is crucial for enhancing diagnostic accuracy. Additionally, in-depth exploration of the potential pathological mechanisms underlying antibody-negative AE, particularly hypotheses concerning blood-brain barrier dysfunction and central nervous system immune responses, will provide new insights into disease mechanisms.

In conclusion, our meta-analysis demonstrates that patients with antibody-negative AE present with a higher age of onset, lower tumor comorbidity rates, and reduced CSF cell counts compared to their antibody-positive counterparts. We also identified regional differences in the incidence of epileptic seizures. These findings not only enhance our understanding of the pathological mechanisms and clinical characteristics of AE but also provide crucial evidence for tailoring individualized diagnostic and therapeutic strategies in clinical practice.

DISCLOSURE

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Conflicts of interest: None

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