Antibody-Negative Autoimmune Encephalitis
A Single-Center Retrospective Analysis

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Abstract

Background and Objectives
Autoimmune encephalitis (AE) refers to a heterogeneous group of inflammatory CNS diseases. Subgroups with specified neural autoantibodies are more homogeneous in presentation, trigger factors, outcome, and response to therapy. However, a considerable fraction of patients has AE features but does not harbor detectable autoantibodies and is referred to as antibody-negative AE. Our aim was to describe clinical features, trigger factors, treatments, and outcome of a cohort of comprehensively tested antibody-negative AE patients.

Methods
This retrospective monocentric study recruited adult patients whose serum and/or CSF was sent to our tertiary center for neural antibody testing between 2011 and 2020, who entered the diagnostic algorithm as possible antibody-negative AE and had the following: (1) probable antibody-negative AE, definite antibody-negative acute disseminated encephalomyelitis (ADEM), or definite autoimmune limbic encephalitis (LE) according to diagnostic criteria; (2) available data on MRI of the brain, CSF, and EEG; and (3) stored serum and/or CSF samples. These samples were reanalyzed using a comprehensive combination of cell-based and tissue-based assays.

Results
Of 2,250 patients tested, 33 (1.5%) were classified as possible antibody-negative AE. Of these, 5 were found to have antibodies by comprehensive testing, 5 fulfilled the criteria of probable AE (3F:2M, median age 67, range 42–67), 4 of definite autoimmune LE (2F:2M, median age 45.5, range 27–60 years), one of definite antibody-negative ADEM, 2 of Hashimoto encephalopathy, one had no samples available for additional testing, and 15 had no further categorization. Of 10 probable/definite AE/LE/ADEM, one had a malignancy and none of them received an alternative diagnosis until the end of follow-up (median 18 months). In total, 80% (8/10) of patients received immunotherapy including corticosteroids, and 6/10 (60%) patients received rituximab, azathioprine, cyclophosphamide, plasma exchange, or IV immunoglobulins. Five (50%) patients improved, one (10%) stabilized, one (10%) worsened, and 3 (30%) died. All deaths were considered to be related to encephalitis. We did not observe differences of immunotherapy-treated patients in likelihood of improvement with or without nonsteroidal immunotherapy (with 2/6, without 1/2).

Discussion
Antibody-negative AE should be diagnosed only after comprehensive testing. Diagnostic effort is important because many patients benefit from immunotherapy and some have malignancies.

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Glossary

ADEM = acute disseminated encephalomyelitis; AE = autoimmune encephalitis; DR2 = dopamine receptor 2; GlyR = glycine receptor; IHC = immunohistochemistry; LE = limbic encephalitis; mGluR5 = metabotropic glutamate receptor 5; mRS = modified Rankin Scale; NCSE = nonconvulsive status epilepticus.

Introduction

Autoimmune encephalitis (AE) can affect children and adults of all ages, manifests with subacute to chronic cognitive dysfunction, often epileptic seizures and sometimes more widespread cerebral/cerebellar/brainstem dysfunction and symptoms of the peripheral/autonomic nervous system dysfunction. It is approximately as frequent as that of infectious origin, with an estimated incidence 0.8/100,000 person-years. Neural autoantibodies targeting intracellular and neural surface antigens have been demonstrated in CSF and serum of many of these patients and have proven to be invaluable biomarkers. Autoantibody-defined AE subtypes are considerably more homogeneous epidemiologically, clinically, and pathophysiologically as well as in tumor associations, therapy response, and outcome. Several large case series of seropositive AE subtypes have sharpened—and sometimes expanded—the clinical picture, provided class III-IV evidence of efficacy of immunosuppressive therapy, and motivated the initiation of first randomized controlled trials.

However, in a considerable proportion of patients with symptoms and findings reminiscent of antibody-positive AE, no neural autoantibodies can be identified and have hence been labeled as antibody-negative AE. In principle, 3—not mutually exclusive explanations—can be considered for antibody-negative AE, with only the first one being "truly" antibody-negative AE sensu stricto: (1) non–autoantibody-associated autoimmunity, e.g. adaptive cell-mediated autoimmune syndromes, innate "autoinflammatory" mechanisms, or neural autoantibodies not detectable by current state-of-the-art screening and confirmation assays; (2) methodological reasons, e.g. not applying stringent classification criteria, not using all available diagnostic tests including screening tests for unknown antigenic targets or examining only serum; and (3) misclassification, e.g. non-inflammatory diseases mimicking AE syndromes. Recent best practice guidelines therefore recommend to exclude patients with "alternative explanations" and to test the samples of suspected antibody-negative AE patients in a research laboratory using comprehensive testing methods before applying the label "antibody-negative." However, the stringent application of these definitions and the methodology of antibody testing varied widely across the available studies. To the best of our knowledge, at the time of preparation of this manuscript, only few studies focusing on antibody-negative AE in adults and stringently adhering to these criteria have been published.

In 2018, Graus et al. reported on a mostly Caucasian–retrospective cohort of 163 patients diagnosed with limbic encephalitis (LE), which included 12 (7%) cases who were antibody-negative even after extensive antibody testing. In comparison with the antibody-positive group, these were mostly older male patients with isolated or predominant short-term memory loss, while psychiatric symptoms and seizures were less common. A majority improved with immunotherapy (IT), highlighting the importance of treatment in this group. In 2022, Lee and colleagues described a mixed, multicentric cohort of Korean AE patients—45% (119 patients) were antibody-positive and 55% antibody-negative (147 patients). The antibody-negative group was divided into probable antibody-negative AE, definite autoimmune LE, and antibody-negative acute disseminated encephalomyelitis (ADEM). Negative prognostic factors (RAPID Score) were refractory status epilepticus, age at onset older than 60 years, probable antibody-negative AE, infratentorial involvement on MRI, and delay of IT >1 month. In 2023, Orozco et al. described a mixed cohort of 361 AE patients with 18 probable antibody-negative AE, 4 antibody-negative ADEM cases, and 102 possible antibody-negative AE not otherwise categorizable. The probable antibody-negative AE group however did not have more specific clinical information, besides 38% of them having seizures and 67% having new focal CNS findings as part of clinical picture.

Our aim was to confirm and possibly extend these observations in a large monocentric, Caucasian, well-characterized cohort with long-term follow-up and stringent application of diagnostic criteria and testing strategies to better counsel physicians and patients. We focused on clinical features, treatment, long-term outcome, and adverse treatment events.

Methods

Patients and Samples

Patient Selection

All patients whose serum and/or CSF samples were tested for the presence of neural autoantibodies at our institution between October 2011 and December 2020 were included (N = 2,612). After exclusion of patients from external institutions and pediatric (younger than 18 years) patients, medical records of 2,250 patients were available for review. Patients’ data were reviewed, and previously published criteria were applied in a stepwise manner as recommended. Clinical categorization was performed consensually by 2 reviewers (H.M. and M.E.); exclusion of alternative causes was based on patients’ medical records. Patients entering the diagnostic flowchart fulfilling the criteria of possible antibody-negative AE were analyzed further.
We used the diagnostic flowchart as recommended by Graus and colleagues. Criteria for possible antibody-negative AE included (1) subacute onset of working memory deficits, altered mental status, or psychiatric symptoms and (2) at least one of new focal CNS findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis, or MRI features suggestive of encephalitis. Criteria for probable antibody-negative AE included (1) subacute onset of working memory deficits, altered mental status, or psychiatric symptoms and (2) at least 2 of MRI abnormalities suggestive of autoimmune encephalitis, CSF pleocytosis, CSF-specific oligoclonal bands or elevated IgG index, or brain biopsy with inflammatory changes. Criteria for definite ADEM included (1) a first multifocal, clinical CNS event of presumed inflammatory demyelinating cause, encephalopathy that cannot be explained by fever; (2) diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter on MRI; and (3) no new clinical or MRI findings after 3 months of symptom onset. Diagnostic criteria for definite autoimmune LE (with negative neural autoantibodies) included (1) subacute onset of working memory deficits, seizures, or psychiatric symptoms; (2) bilateral brain MRI abnormalities (increase in signal intensity in T2-weighted sequences) highly restricted to the medial temporal lobes; and (3) at least one of CSF pleocytosis or EEG with abnormal activity involving the temporal lobe(s).

**Data Acquisition**

The predefined data set included demographics (age, sex), symptoms of working memory deficit, altered mental status, psychiatric symptoms, seizures, cognitive deficit (in domains besides working memory), and focal CNS signs (e.g., extrapyramidal symptoms, cerebellar symptoms, limb paresis). Modified Rankin Scale (mRS) and CASE score were different at time points assessed retrospectively from medical records (during hospitalization, at discharge, in the first 9 months after symptom onset, at the last follow-up on-site or by phone for mRS, on-site for CASE). Improvement or worsening of mRS and CASE scores was defined by a change of 1 or more points both at discharge (initial improvement/worsening) and at the last follow-up (sustained improvement/worsening), and stabilization was noted when there was no change of score. Improvement, independent of IT, was defined as minus 1 or more points in mRS and CASE in a patient who did not receive immunomodulating treatment. RAPID score was also noted retrospectively for each patient with available data, with values of 0–1 reported to be predictive of good outcome (mRS 0–2) and 2–5 reported to be predictive of poor outcome (mRS 3–6). Autoimmune comorbid conditions were noted in all patients.

All patients had MRI, EEG, and CSF studies done. EEG patterns were classified according to the presence of focal (unilateral or bilateral) or diffuse slowing, epileptiform activity and electrographic seizures including nonconvulsive status epilepticus (NCSE). The first recorded EEG at our institution and the preceding EEG at an external institution, if available, were evaluated. MRI patterns were divided into LE (T2/fluid attenuation inversion recovery [FLAIR] increase in signal intensity highly restricted to one or both medial temporal lobes) or multifocal (multiple lesions in white and/or gray matter compatible with demyelination or inflammation). CSF analysis included all standard investigations. Abnormal CSF was the presence of any of the following: pleocytosis (>4 cells/μL), increased protein (range according to age), albumin (range according to age), IgG (>40 mg/L), IgM (>1.3 mg/L), increased albumin index (QAlb >9.9), intrathecal synthesis of IgG based on IgG index, and/or presence of oligoclonal bands on isoelectric focusing. When multiple lumbar punctures were done, CSF leukocyte count and oligoclonal bands were chosen from the sample with the highest count.

AE was considered paraneoplastic if a malignant tumor was diagnosed up to 5 years before or after diagnosis, or there was a recent progression of a previously well-controlled malignancy.

Cutoff for early vs late IT administration was set to 28 days from the onset of symptoms.

**Antibody Testing Strategy**

All patients’ samples (serum and CSF) were routinely tested using commercially available kits: cell-based assays (CBA) (Autoimmune Neurology Mosaic 1, EUROIMMUN, Lübeck, Germany, testing NMDAR, a-aminohexy-5-methyl-4-isoxazolepropionic acid receptor subunit 1 and 2, contactin-associated protein 2, leucine-rich glioma-inactivated protein 1, gamma-aminobutyric acid B-receptor) and immunoblots (PNS11 Line assay, ravo Diagnostika, Freiburg, Germany, including Hu, Yo, Ri, CV2/CRMP5, Amphiphysin, Ma1 and 2, SOX1, glutamic acid decarboxylase 65, Tr/DNER and Zic4 or EUROLINE PNS 12 Ag, EUROIMMUN, Lübeck, Germany, including recoverin, PKCy, and titin in addition) (see eTables 1 and 2, links.lww.com/NXI/A916, links.lww.com/NXI/A917). Cases with borderline or low positivity titer on line-blot in serum sample considered as unrelated to the clinical picture (e.g. anti-Yo in a male with LE) were considered antibody-negative. All samples were kept in aliquots frozen at −80°C until further analysis. Patients without samples (obtained during the active phase of disease) available for further testing were excluded from the study.

Samples from all patients entering the diagnostic flowchart of possible antibody-negative AE underwent further testing during the study using (1) live CBA on nonpermeabilized full-length human MOG-transfected HEK293T cells (Alexa 564 conjugated anti-human IgG H + L) for the detection of anti-MOG antibodies in serum and (2) tissue-based indirect immunohistochemistry (IHC) on rat brain slices as screening assays for rare autoantibodies as previously described. Positivity was always rated by 2 examiners (H.M. and F.L. or J.D.). These (and the tests below) were performed at the Neuroimmunology Laboratory of the Institute for Clinical Chemistry, Kiel, Universitätsklinikum Schleswig-Holstein, Germany.
All samples testing positive on rat brain immunohistochemistry underwent further testing using (1) human embryonic kidney 293T cells transfected with plasmid coding for γ-aminobutyric acid-A receptor (GABA-AR), glycine receptor (GlyR), dopamine receptor 2 (DR2), metabotropic glutamate receptor 5 (mGluR5), neurexin3α, and IgLON5 on fixed assays and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) on a live assay to search for characterized rare autoantibodies and (2) indirect immunofluorescence assays using live, nonpermeabilized, rat hippocampal neuronal cultures as described previously to identify putative neuronal cell surface staining.26,30 For this study, we categorized samples as positive for unknown neural autoantibodies if (1) we observed a hippocampal staining on indirect rat brain immunohistochemistry (independent of whether in serum and/or CSF) and (2) confirmed neuronal surface staining using live embryonal neuron cultures.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The study was approved by the Ethics Committee of Motol University Hospital in Prague. The study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients agreed to have their CSF and serum samples stored for further research use.

Informed consent was obtained from all participants in this study, except the deceased patients.

**Statistical Analysis**

Descriptive statistical analysis was performed using Minitab software (version 21.2, 2022). Continuous variables were expressed as mean (SD) when in normal distribution or as median (range) when the distribution was shown to be not normal by normality testing and categorical variables as percentages or range. Comparing the 2 groups was performed using the Fisher exact test for categorical variables. The significance level was set to $p = 0.05$.

**Data Availability**

Anonymized data not published within this article will be made available by request from any qualified investigator.
Table 1 Clinical Characteristics and Supportive Findings in Patients Fulfilling the Criteria for Probable Antibody-Negative AE and Definite ADEM

<table>
<thead>
<tr>
<th>No</th>
<th>Age/sex</th>
<th>Symptoms</th>
<th>MRI brain</th>
<th>CSF results* (1st, 2nd and last sample if available)</th>
<th>EEG</th>
</tr>
</thead>
</table>
| 1  | 67/F    | Altered mental status, memory loss, cognitive deficit | WM lesions compatible with inflammation/demyelination | 1ª: leuko normal, TP 1280, IgG index NA, OCB 2.0  
2ª: leuko 16, TP 460, IgG index + OCB 0/0  
L: leuko 3, TP 425, IgG index negative, OCB NA | Possible NCSEb; EPFA left, intermittent slow bilat, PDR slowing |
| 2ª | 67/F    | Altered mental status, memory loss, cognitive deficit | WM lesions compatible with inflammation/demyelination | 1ª: leuko 1,280, TP 1370, IgG index + OCB NA  
2ª: leuko 123, TP 1400, IgG index negative, OCB 20/0  
L: leuko 23 (mixed pleocytosis), TP 1025, OCB 0/0 | Periodic discharges of triphasic morphology; continuous generalized slow, absent PDR |
| 3  | 67/M    | Altered mental status, memory loss, cognitive deficit, aphasia | Unilateral ISI in MTL | 1ª: leuko 60, TP 463, IgG index + OCB NA  
2ª: leuko 47, TP 708, IgG index +, OCB NA  
L: leuko 19, TP 560, IgG index 8%, OCB 12/0 | Intermittent slow T left, difficult due to abundant AF |
| 4ª | 42/M    | Psychiatric symptoms, focal seizures (pilomotor), gait instability, dysautonomia, movement disorder, diplopia | Unilateral ISI in MTL | 1ª: leuko 42, TP 700, IgG index NA, OCB 14/0  
2ª: leuko 41, TP 660, IgG index 31%, OCB 6/0  
L: leuko 16, TP 460, IgG index 23%, OCB 10/2 | Sporadic EPFA T right; continuous generalized slow accentuated over T regions |
| 5  | 67/F    | Altered mental status, memory loss, psychiatric symptoms, hemiparesis, aphasia | WM lesions compatible with inflammation/demyelination, contrast enhancement cortically | 1ª: leuko 7 (lymphocytic), TP 290, IgG index 78%, OCB 13/0  
2ª: leuko 3, TP 455, IgG index 82%, OCB 8/0 | Mild slowing of PDR frequency |
| 6ª | 60/M    | Altered mental status, psychiatric symptoms, memory loss, cognitive deficit, apraxia, right hemiparesis | WM lesions compatible with inflammation/demyelination | 1ª: leuko NA but not pleocytosis, TP 1170, IgG index + OCB NA  
2ª: leuko NA, TP 1799, IgG index + OCB NA  
L: leuko 8, TP 700, IgG index negative, OCB 5/5 | Intermittent slow T bilat (independent) |

Abbreviations: AF = artifacts; bilat = bilateral; EPFA = epileptiform activity; F = frontal; FBTCs = focal to bilateral tonic-clonic seizures; FIRD = frontal intermittent rhythmic delta activity; F-T = frontotemporal; ISI = increased signal intensity; L = last; leuko = leukocytes per mm³; MTL = medial temporal lobes; NA = not applicable; NCSE = nonconvulsive status epilepticus; O = occipital; OCB = oligoclonal bands; PDR = posterior dominant rhythm; T = temporal; T-O = temporal-occipital; TP = total protein; WM = white matter.

ª This patient was suspected on IHC screening, but not confirmed with in-house HEK cells or neuronal cell culture CBAs.
ªª Analysis done at external institution.
ª This patient had a brain biopsy with signs consistent with encephalitis (active lymphocytic meningoencephalitis mostly cortically, without signs of vasculitis, no viral inclusions).
ª This patient had high-titer antibodies detected only with comprehensive testing during this study, leading to reclassification as antibody-positive AE. Two of these 5 only fulfilled the initial criteria of possible antibody-negative AE with no further subcategorization using the diagnostic algorithm. Of these 5 patients, 1 had GlyR antibodies in serum and 4 had uncharacterized neuronal surface antibodies confirmed by IHC and staining of nonpermeabilized, live primary embryonal neuronal murine cultures (n = 1 CSF, n = 1 CSF and serum, n = 2 only in serum). Two further patients had borderline positive findings using live cell-based MOG antibody testing (1:40 or 1:80, cutoff 1:160) considered nonspecific. No patients had high-titer MOG antibodies in their serum.
ª Total protein in milligrams per liter, cells per 1 μL, OCBs in CSF/serum.
ª Total protein in milligrams per liter, cells per 1 μL, OCBs in CSF/serum.

Results

Patient Selection

Of 2,250 patients, 62 (2.8%) were classified as antibody-positive AE. Of these, 57 (92%) had neural autoantibodies detected using widely applied commercially available antibody assays (anti-NMDAR encephalitis n = 19, anti-LGI1 encephalitis n = 18, anti-CASPR2 encephalitis n = 5, anti-GAD encephalitis n = 3, anti-Ma2 encephalitis n = 3, anti-Hu encephalitis n = 2, anti-AMPAR encephalitis n = 1, anti-GABA-B-receptor encephalitis n = 1, and encephalitis syndromes with multiple autoantibodies n = 5). Twenty-five of these (40%) had the phenotype of LE with supportive brain MRI findings. The 5 remaining seropositive patients (8% of the seropositive group) had neural autoantibodies in CSF and/or serum detected only with comprehensive testing during this study, leading to reclassification as antibody-positive AE. Two of these 5 only fulfilled the initial criteria of possible antibody-negative AE with no further subcategorization using the diagnostic algorithm. Of these 5 patients, 1 had GlyR antibodies in serum and 4 had uncharacterized neuronal surface antibodies confirmed by IHC and staining of nonpermeabilized, live primary embryonal neuronal murine cultures (n = 1 CSF, n = 1 CSF and serum, n = 2 only in serum). Two further patients had borderline positive findings using live cell-based MOG antibody testing (1:40 or 1:80, cutoff 1:160) considered nonspecific. No patients had high-titer MOG antibodies in their serum. Additional 2 (0.1%) patients were classified as Hashimoto encephalopathy, and one patient was excluded due to unavailability of samples (see Figure 1).
Table 2 Therapy and Outcomes in Patients Fulfilling the Criteria for Probable Antibody-Negative AE and Definite ADEM

<table>
<thead>
<tr>
<th>No</th>
<th>Autoimmunity/Tumor (time to Dx*)</th>
<th>Immunotherapy (time from 1st line administered)</th>
<th>Time to Dx b,d</th>
<th>ASM*</th>
<th>mRS, CASE* at admission/discharge/in the next 9 months/last FU</th>
<th>RAPID score</th>
<th>Time to last FU*, reason for death if deceased (autopsy results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0/0</td>
<td>i.v. SM 6g, CSM (dose NA) (77) NA (&lt;60)</td>
<td>NA (&lt;60)</td>
<td>LEV, VPA, LCM, BRV</td>
<td>5/4/3/3; 11/5/NA/6</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>2a</td>
<td>0/0</td>
<td>i.v. SM 5g, CSM 1g (100) 100</td>
<td>0</td>
<td>LEV, VPA, PER</td>
<td>5/5/6/6; 19/17/D/D</td>
<td>3</td>
<td>5, reason: probably encephalitis related - bedridden (NA)</td>
</tr>
<tr>
<td>3</td>
<td>0/0</td>
<td>i.v. SM 5g + p.o. taper (21) 13</td>
<td>0</td>
<td>2/1/0/0; 3/2/1/0</td>
<td>2</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>4i</td>
<td>Chronic autoimmune thyroiditis/0</td>
<td>i.v. SM 2 × 5g + p.o. taper, PE 5×, CSM 3 × 1,5g, RTX 3× (30) 14</td>
<td>2/2/4/6; 7/7/7/D</td>
<td>GBP, PGB, PHT, LCM, LEV, CLB</td>
<td>2</td>
<td>15, reason: probably encephalitis related - bedridden (NA)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Graves-Basedow thyroiditis/NA</td>
<td>i.v. SM 5g (8) 2</td>
<td>LEV</td>
<td>5/6/6/6; 11/D/D/D</td>
<td>3</td>
<td>0, reason: probably encephalitis related - bedridden, aspiration pneumonia (NA)</td>
<td></td>
</tr>
<tr>
<td>6i</td>
<td>0/0</td>
<td>i.v. SM 3g + p.o. taper, AZT 75 mg daily (&lt;80)</td>
<td>NA (&lt;30)</td>
<td>0</td>
<td>4/3/2/2; 10/6/3/3</td>
<td>3</td>
<td>70*</td>
</tr>
</tbody>
</table>

Abbreviations: ADEM = acute disseminated encephalomyelitis; AE = autoimmune encephalitis; Abs = antibodies; ASM = antiseizure medications; AZT = azathioprine; BRV = brivaracetam; CBZ = carbamazepine; CSM = cyclophosphamide; Dx = diagnosis; FU = follow-up; GBP = gabapentin; i.v. = IV; IgG = immunoglobulin G; IVIG = IV immunoglobulin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; NA = data not available; p.o. = peroral; PE = plasmapheresis; PGB = pregabalin; PHT = phenytoin; RTX = rituximab; SM = SoluMedrol; VPA = valproic acid.  
* Definite antibody-negative ADEM.  
† In days.  
‡ In months.  
§ In deceased patients, scoring was not possible, marked with D; CASE was only rated during physical follow-up, not by phone.  
¶ Used in total.  
‖ mRS assessment by phone.  
¶ This patient had a brain biopsy with signs consistent with encephalitis (active lymphocytic meningoencephalitis mostly cortically, without signs of vasculitis, no viral inclusions).

Focusing on antibody-negative AE, 25 (1.1%) patients fulfilled the criteria of possible antibody-negative AE, including reasonable exclusion of alternative causes of their symptoms (35% of 72 patients in the combined antibody-positive and antibody-negative AE cohorts). Of these, 10 (0.4% of total cohort) patients were further classified as probable antibody-negative AE (n = 5, 50%), definite ADEM (n = 1, 10%), or definite autoimmune LE (n = 4, 40%) (see Figure 1). MRI of the brain was abnormal in all these patients. Four patients had multiple, asymmetric subcortical, demyelinating lesions (see eFigure 3, links.lww.com/NXI/A915); one of these (#5) had cortical gadolinium enhancement. MOG antibodies were not detectable in any of their sera. Only one of these patients (#6) had stable clinical and MRI findings fulfilling the criteria for definite ADEM. All 4 patients had late age of onset (older than 60 years) considered atypical for ADEM.

Probable Antibody-Negative Autoimmune Encephalitis and Definite ADEM

Five patients (3 female patients) with a median age 67 years (42–67) fulfilled the criteria for probable antibody-negative AE, and one male patient was classified as definite ADEM (see Tables 1 and 2). All patients had a polysymptomatic course (see eFigure 1, links.lww.com/NXI/A913), and the median number of the aforementioned symptom categories was 4 (range 3–6). Altered level of consciousness was present in 6, psychiatric symptoms in 4, memory loss in 4, and seizures in 3 patients. One patient had a history of status epilepticus. Cognitive deficit (domains other than memory affected) was seen in 5 patients, and 4 had other symptoms. The time interval between first manifestation and diagnosis reached a median of 14 days (range 2–100).

CSF was abnormal in all cases. All patients had increased CSF white blood cell count, and the median was 29 cells per mm³ (range 7–1,280). Positive IgG index was seen in CSF of 4/6 and 2 or more CSF-restricted oligoclonal bands in 5/6 patients. In 5 patients, cancer screening was performed; no malignancy was found.

All patients were treated with IT. Two received IT within 4 weeks after symptom onset. All were treated with IV corticosteroids, and 4 (67%) of whom received additional treatments (n = 1 plasmapheresis, n = 1 rituximab, n = 3 cyclophosphamide, and n = 1 azathioprine) (see Table 2). The median time of follow-up in 5 patients who were alive at discharge was 15 months (range 5–70). The median modified Rankin Scale of patients was 4.5 at admission (range 2–5), 3.5 at discharge (range 1–6), 3.5 at 9 months (range 0–6), and 4.5 at the last follow-up (range 0–6) (Figure 2).
At the last follow-up, 3 patients had improved and 3 patients (3/5 with probable antibody-negative AE) had died. Judging severity of AE by reduction in CASE scores, all 3 patients which improved by mRS improved by CASE as well (see Table 2 and Figure 2). Only 1 patient was followed up for at least 2 years; his RAPID score was discordant with mRS (low RAPID corresponded to low mRS19 and vice versa).

**Definite Antibody-Negative Autoimmune Limbic Encephalitis**

Four patients (2 female) with a median age 45.5 years (range 27–60) fulfilled the criteria for definite autoimmune LE (see Tables 3 and 4). All patients had a polysymptomatic course (see eFigure 2, links.lww.com/NXI/A914), and the median number of symptoms was 3.5 (range 2–5). Psychiatric symptoms occurred in 4 patients, memory loss in 3 patients, seizures in 3 patients, and altered level of consciousness in 1 patient. None of the patients had a history of status epilepticus. Cognitive deficit (domains other than memory affected) was seen in 1 patient, and 2 had other symptoms. The time interval between first manifestation and diagnosis reached a median of 59 days (range 20–254).

MRI was abnormal in all 4 patients by definition—with bilateral lesions highly restricted to medial temporal lobes.

CSF was abnormal in all cases. All patients had increased CSF white blood cell count; however, in one case, the exact number of cells was not available. The remaining 3 patients had 23, 40, and 80 cells per mm3. IgG index was negative in all cases, and 2 or more CSF-restricted oligoclonal bands were present in one.

One patient had an already known tumor (breast carcinoma without generalization), 2 other patients had negative malignancy screening, and one had no screening done.

Two patients received IT—both received IV corticosteroids and additional therapy (n = 1 IV immunoglobulins, n = 1 azathioprine). Two patients did not receive IT; both

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**Figure 2** Modified Rankin Scale and CASE Scores in Probable Antibody-Negative AE or ADEM (A–B) and Definite Autoimmune LE (C–D)

A. mRS in probable antibody-negative AE and definite ADEM

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>At admission</th>
<th>At discharge</th>
<th>In first 9 months</th>
<th>At last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

B. CASE score evolution in probable antibody-negative AE and definite ADEM

C. mRS in definite autoimmune LE

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>At admission</th>
<th>At discharge</th>
<th>In first 9 months</th>
<th>At last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

D. CASE score evolution in definite autoimmune LE

---

ADEM = acute disseminated encephalomyelitis; AE = autoimmune encephalitis; mRS = modified Rankin Scale; LE = limbix encephalitis.
improved (Table 4, cases #2 and #3) yet sufficient follow-up (68 months) was only available in 1 of the 2 patients.

The median time of follow-up in these patients was 39.5 months (range 10–68 months) was only available in 1 of the 2 patients.

The median time of follow-up in these patients was 39.5 months (range 0–68). The median modified Rankin Scale of patients was 3 at admission (range 2–4), 2 at discharge (range 1–4), 1.5 at 9 months (n = 2, range 1–2), and 2 at the last follow-up (n = 3, range 1–4) (see Figure 2). Compared with admission, at the last follow-up (n = 3), 1 patient had improved, 1 patient stayed stable, and 1 patient worsened. Judging the severity of AE by reduction in CASE scores, all 4 patients improved (see Table 4 and Figure 2). Three patients were followed up for at least 2 years; RAPID score was concordant with mRS in 2 cases and discordant in 1 case.

**Table 3** Clinical Characteristics and Supportive Findings in Patients Fulfilling the Criteria for Definite Autoimmune LE

<table>
<thead>
<tr>
<th>No</th>
<th>Age/sex</th>
<th>Symptoms</th>
<th>MRI brain</th>
<th>CSF results (1st, 2nd, and last sample if available)</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60/F</td>
<td>Psychiatric symptoms, memory loss, severe cognitive deficit, focal seizures</td>
<td>Bilateral ISI in MTL</td>
<td>1°:leuko 16 (lymphocytic),TP 408, IgG index + OCB NA; 2°:leuko 23 (lymphocytic), TP 500, IgG index + OCB 0/0</td>
<td>Abundant EPFA O left and independently T-O right; intermittent generalized slow with left predominance</td>
</tr>
<tr>
<td>2</td>
<td>55/M</td>
<td>Psychiatric symptoms, gait instability, bulbar syndrome, vertigo, diplopia</td>
<td>Bilateral ISI in MTL</td>
<td>1°:leuko 34, TP NA, IgG index + OCB NA; 2°:leuko 80, TP 150, IgG index negative, OCB 2/0; L:leuko 17, TP 1300, IgG index negative, OCB 2/2</td>
<td>Intermittent slow T left</td>
</tr>
<tr>
<td>3</td>
<td>27/F</td>
<td>Psychiatric symptoms, memory loss, focal seizures and FBTCs</td>
<td>Bilateral ISI in MTL</td>
<td>1°:leuko 40, TP NA, IgG index + OCB NA; 2°:leuko 1, TP 175, IgG index + OCB 0/0</td>
<td>FIRA DA, abundant focal slow T bilat, mild slowing of PDR frequency</td>
</tr>
<tr>
<td>4*</td>
<td>36/M</td>
<td>Altered mental status, psychiatric symptoms, memory loss, focal seizures</td>
<td>Bilateral ISI in MTL</td>
<td>1°:leuko pleocytosis (NA exact number), TP NA, IgG index + OCB NA; 2°:leuko 1, TP 400, IgG index + OCB 0/0</td>
<td>EPFA and focal slow (unspecified)*, intermittent focal slow F/FT bilat</td>
</tr>
</tbody>
</table>

Abbreviations: bilat = bilateral; EPFA = epileptiform activity; F = frontal; FBTCs = focal to bilateral tonic-clonic seizures; FIRA DA = frontal intermittent rhythmic delta activity; F-T = frontotemporal; ISI = increased signal intensity; L = last; leuko = leukocytes per mm3; LE = limbic encephalitis; MTL, medial temporal lobes; NA = not applicable; NCSE = nonconvulsive status epilepticus; O = occipital; OCB = oligoclonal bands; PDR = posterior dominant rhythm; T = temporal; T-O = temporo-occipital; TP = total protein; WM = white matter.

*This patient was suspicious on IHC screening but not confirmed with in-house HEK cells or neuronal cell culture CBAs.

b Analysis done at external institution.

c Total protein in milligrams per liter, cells per one μL, OCBs in CSF/serum.

**Table 4** Therapy and Outcomes in Patients Fulfilling the Criteria for Definite Autoimmune LE

<table>
<thead>
<tr>
<th>No</th>
<th>Autoimmunity/Tumor (time to Dx)*</th>
<th>Immunotherapy (time from 1st line administered)*</th>
<th>Time to Dx**</th>
<th>ASM**</th>
<th>mRS, CASE*: at admission/discharge/in the next 9 months/last FU</th>
<th>RAPID score</th>
<th>Time to last FU*, reason for death if deceased (autopsy results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O/breast carcinoma^ (4m)</td>
<td>i.v. SM 5g + p.o. taper, IVIG 175g (184)</td>
<td>20</td>
<td>LEV, LCM</td>
<td>3/3/NA/4; 6/5/NA/NA</td>
<td>2</td>
<td>34^</td>
</tr>
<tr>
<td>2</td>
<td>O/NA</td>
<td>0</td>
<td>59</td>
<td>0</td>
<td>3/1/1/1; 6/2/1/NA</td>
<td>3</td>
<td>68^</td>
</tr>
<tr>
<td>3</td>
<td>O/0</td>
<td>254</td>
<td>0</td>
<td>LTG, PHT, LEV, CBZ</td>
<td>4/2/NA/NA; 6/5/NA/NA</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4*</td>
<td>Sarcoidosis/0</td>
<td>i.v. SM (dose NA), AZT (100mg daily) (~30)</td>
<td>4/2/2/2; 5/5/2/2</td>
<td>LEV, LCM</td>
<td>2/2/2/2; 5/5/2/2</td>
<td>1</td>
<td>45^</td>
</tr>
</tbody>
</table>

Abbreviations: Abs = antibodies; ASM = antiseizure medications; AZT = azathioprine; BRV = brivaracetam; CBZ = carbamazepine; CLB = clobazam; CSM = cyclophosphamide; Dx = diagnosis; FU = follow-up; GBP = gabapentin; i.v. = intravenous; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; LCM = lacosamide; LE = limbic encephalitis; LTG = lamotrigine; NA = data not available; p.o. = peroral; PE = plasmapheresis; PGB = pregabalin; PHT = phenytoin; RTX = rituximab; SM = SoluMedrol; VPA = valproic acid.

*From the first day of month of onset to the day of Abs testing.

^CASPR2 positive in serum at a different institution with unknown titre, retested at our institution as negative (end point titre 1:10).

^Breast carcinoma treated surgically, with no further radiotherapy, hormonal therapy or chemotherapy, FDG-PET/CT negative.

*In days.

^In months.

^In deceased patients, scoring was not possible, marked with D; CASE was only rated during physical follow-up, not by phone.

^Used in total.

^mRS assessment by phone.
Possible Antibody-Negative Autoimmune Encephalitis Without Further Subcategorization

We have also looked at patients who entered the diagnostic flowchart by having possible antibody-negative AE but who did not fulfill any of the further diagnostic criteria. Seventeen initially entered this classification, but 2 were found to be antibody-positive after comprehensive testing (see Figure 1). Therefore, this group consisted of 15 patients, the median age was 62 years (24–82), and 53% were female. MRI of the brain was abnormal in 7 (47%) patients. Inflammatory CSF was seen in 5 (33%) patients. Pleocytosis was seen in 4 of the CSF samples. IgG index and oligoclonal bands were measured for 14 patients—IgG index was positive in 1 and CSF-specific oligoclonal bands in 2 patients. None of the patients had a brain biopsy. Seven of 13 patients with oncological screening performed had a malignancy. Nine (60%) patients were treated with IT—al with IV corticosteroids. In 3 (33%) patients, additional immunotherapy was used (one of each: IV immunoglobulins, cyclophosphamide, and azathioprine). Seven of the treated patients (78%) improved initially, and 3 of 6 with further follow-up had sustained improvement. Ten (67%) patients have died.

Cause of Death and Association of Immunotherapy With Outcome in Antibody-Negative AE

Next, we analyzed the combined cohort of probable antibody-negative AE, definite ADEM, and definite autoimmune LE for the likelihood of improvement in the subgroup of patients treated with additional nonsteroidal IT; the overall mortality, cause of death, and its relationship to tumor, encephalitis, or infection. We did not observe differences in likelihood of improvement in patients with or without nonsteroidal IT (with 2/6, without 1/2, \( p = 1.0 \), Fisher exact test).

Only 1 patient, with definite autoimmune LE, had a potential paraneoplastic etiology (breast carcinoma diagnosed 4 months before AE). This patient survived with an mRS of 4 at the last follow-up.

Overall, 3/10 patients died (30%). Mortality was higher in patients with probable antibody-negative AE (60%, 3/5, none of these had accompanying tumors) compared with no patients with definite autoimmune LE (0/4, \( p = 0.4 \), Fisher exact test). All 3 deaths were considered related to encephalitis.

Discussion

We report on clinical features, therapy, outcome, mortality, and cause of death in a retrospective, monocentric cohort of 10 patients with antibody-negative AE. Our main findings are that (1) 14% of patients classified as autoimmune encephalitis were indeed antibody-negative even after comprehensive testing. Five patients (2 of those possible antibody-negative AE only) initially considered antibody-negative after using widely applied “routine” commercial test assays were recategorized as antibody-positive underlining the importance of comprehensive test strategies. (2) Most patients with antibody-negative AE were older (median age 60 years for the whole cohort), without a clear gender predominance. (3) Concurrent malignancies were not common (12.5% of the screened patients). (4) Most patients (80%) were treated with IV corticosteroids, and 60% of these patients received additional IT. Of patients treated with IT, 50% showed improvement on the last follow-up. However, we did not observe differences in response to therapy between patients with or without nonsteroidal IT. (5) Outcome was better in patients classified as definite autoimmune LE with negative neural autoantibodies than in patients with probable antibody-negative AE. This was mainly due to higher overall mortality in patients with probable antibody-negative AE (60% vs 0%). The cause of death was encephalitis-associated morbidity in all patients.

Of note, 4/10 patients had multifocal white matter (in 1 case also cortical) demyelination together with focal neurologic signs and encephalopathy. At the time of diagnosis, all 4 patients’ MRIs were compatible with ADEM, yet 3 patients deteriorated, thus not fulfilling the current criteria of ADEM requiring absence of new clinical or MRI worsening after 3 months. In addition, 2/4 patients died within a few months, which is also atypical for ADEM. Whether these had primarily antibody-negative glial (ADEM) or some overlap of neuronal and glial autoimmunity remains unclear. There were 17 patients who entered the diagnostic algorithm by being categorized as possible antibody-negative AE but who had no further subcategorization. Although one has to be careful when analyzing this heterogenous group, we decided to investigate these patients as well. As mentioned, 2 had positive antibodies by comprehensive testing and were thus reassessed as antibody-positive. Of note, the algorithm does not suggest to test such patients further in a research laboratory, and these patients would have been missed if the algorithm was strictly followed. The remaining 15 patients often had tumors (54% of screened patients), and many responded to IT (78% at least transiently).

Our cohort was considerably smaller than the recently published study by Lee and colleagues of 147 antibody-negative AE patients. Patients in our cohort were older (median age 60 years compared with 40 years), and we observed a smaller fraction of antibody-negative patients (14% vs 55%) possibly due to our more comprehensive testing strategy and the different ethnicity. Their study did not evaluate the presence of tumors in these patients; in our series, 1 of 10 (8 screened) patients had a tumor. Most likely because of different center-specific treatment strategies, fewer patients in our cohort received rituximab/cyclophosphamide-based immunosuppression (12.5% vs 78.5%). Therefore, we were unable to perform any statistical analysis except for descriptive statistics. Nevertheless, despite less usage of “second-line” immunotherapy, the overall rate of favorable outcome (mRS 0–2) at the final follow-up in our cohort of antibody-negative AE (50%) was comparable with the frequency in the Korean series (56.5% at two years). In addition, we could not find significant differences in the outcome of patients treated with nonsteroidal immunosuppression compared with patients who were treated with corticosteroids only. Of
note, both observations should not be considered to imply firm evidence of the absence of nonsteroidal immunomodulatory treatment effects in patients with antibody-negative AE. Rather, it should caution against treating patients in a “one-size-fits-all” manner because not all patients might need intensive immunosuppression and spontaneous improvement does occur17,33 (as also observed in 2 patients from our cohort). Thus, individualized treatment decisions in these, often older, patients should be sought and based on the syndrome, findings, and associated comorbidities, especially associated tumors. Although a lower percentage of our patients had tumors (10%), paraneoplastic etiology should be carefully considered, especially in definite autoimmune LE (25% had associated tumors). Patients died from progressive encephalitis and consecutive morbidity and immobility leading to infectious complications, which is well known for antibody-positive paraneoplastic syndromes, e.g. anti-Hu syndrome.54 Concomitant IT might have played a role in infectious complications as well. For immunotherapy, utmost care should be taken in choice and length of treatment especially in the older and paraneoplastic patients in whom the danger lies on both sides: immunosuppressive overtreatment and undertreatment can both be dangerous.

A previous case series described 12 patients with definite autoimmune LE with negative neural autoantibodies (12/163 patients, 7%), mostly older men with leading or isolated symptom of memory loss and seizures were observed rarely, and paraneoplastic etiology was common (42%).18 In our case series, we observed 14% definite autoimmune LE patients (4/29). A paraneoplastic etiology was seen in 1 patient with nonmetastatic breast carcinoma treated with surgery (25%). We did not observe gender predominance (50% male), and the age range was 27–60 years. Memory loss was seen in 3 (75%) and seizures in 75%; but in all, other symptoms were present as well. This incongruence is most likely a sampling bias in both series.

A major strength of our case series is the comprehensive test strategy including screening with tissue immunohistochemistry, which resulted in the detection of 5 patients as antibody-positive (3 of probable, 2 only of possible antibody-negative AE criteria), which would otherwise have been considered antibody-negative and skewed the case series considerably. This is in contrast to most published cases on antibody-negative AE.16,18,35-37 Of note, although none of our patients had progressive encephalomyelitis with rigidity and myoclonus (PERM) phenotype, we have not tested GlyR antibodies in all patients, possibly missing some antibody-positive cases. The main limitation of our study concerns the imminent sampling and reporting bias of retrospective case series. Furthermore, the study was subject to selection bias because we were only studying patients whose samples were sent for antibody testing—some cases might have been missed and not referred for testing. Yet as a tertiary reference/referral center in Czechia, we are likely to have an almost complete picture of our country—most (7/10, 70%) of the included patients diagnosed or initially managed elsewhere were later consulted with or transferred to our hospital. Considering specificity, one of the excluded patients would—at the time of their initial symptoms—fulfill the criteria of probable antibody-negative AE and was only postmortem identified to suffer from Creutzfeldt-Jakob disease (CJD). Taking this further, we cannot rule out that some of the deceased patients without autopsy studies were not in fact patients with CJD or other mimics of AE.

In conclusion, our study outlines clinical presentation of antibody-negative AE, warns of the considerable mortality, and highlights the importance of comprehensive antibody testing in cases with suspected antibody-negative AE, even in patients who do not fulfill the criteria of probable antibody-negative AE but have 1 of the 2 criteria of inflammation (CSF or MRI) fulfilled. Especially in those without a clear response to first-line immunotherapy, the results of antibody tests can strongly influence further decision-making on proceeding to more aggressive treatments.58 Furthermore, research laboratory testing in suspected cases could lead to the detection of novel antibodies. For future studies on antibody-negative AE, we suggest TBAs to be included in the neural autoantibody testing when antibody-negative cases of AE are described.

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Antibody-Negative Autoimmune Encephalitis: A Single-Center Retrospective Analysis
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