

# Autoimmune Encephalitis Criteria in Clinical Practice

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## Abstract

### Background and Objectives

To assess the clinical practice applicability of autoimmune encephalitis (AE) criteria (2016).

### Methods

Medical records of 538 adults diagnosed with AE or related autoimmune encephalopathy at Mayo Clinic (not including pure movement disorders) were reviewed and AE guideline criteria applied.

### Results

Of 538 patients, 288 were male (52%). The median symptom onset age was 55 years (range, 11–97 years; 16 had onset as children). All had other non-AE diagnoses reasonably excluded. Of 538 patients, 361 (67%) met at least possible criteria, having all 3 of subacute onset; memory deficits, altered mental status or psychiatric symptoms, and  $\geq 1$  supportive feature (new focal objective CNS finding, N = 285; new-onset seizures, N = 283; supportive MRI findings, N = 251; or CSF pleocytosis, N = 160). Of 361 patients, AE subgroups were as follows: definite AE (N = 221, 61%, [87% AE-specific IgG positive]), probable seronegative AE (N = 18, 5%), Hashimoto encephalopathy (N = 20, 6%), or possible AE not otherwise categorizable (N = 102, 28%). The 221 patients with definite AE had limbic encephalitis (N = 127, 57%), anti-NMDA-R encephalitis (N = 32, 15%), ADEM (N = 8, 4%), or other AE-specific IgG defined (N = 54, 24%). The 3 most common definite AE-IgGs detected were as follows: LGI1 (76, 34%), NMDA-R (32, 16%), and high-titer GAD65 (23, 12%). The remaining 177 patients (33%) not meeting possible AE criteria had the following: seizures only (65, 12% of all 538 patients), brainstem encephalitis without supratentorial findings (55, 10%; none had Bickerstaff encephalitis), or other (57, 11%). Those 57 “others” lacked sufficient supportive clinical, radiologic, or CSF findings (N = 26), had insidious or initially episodic onset of otherwise typical disorders (N = 21), or had atypical syndromes without clearcut memory deficits, altered mental status, or psychiatric symptoms (N = 10). Fifteen of 57 were AE-specific IgG positive (26%). Among the remaining 42, evidence of other organ-specific autoimmunity (mostly thyroid) was encountered in 31 (74%,  $\geq 1$  coexisting autoimmune disease [21, 50%] or  $\geq 1$  non-AE-specific antibodies detected [23, 53%]), and all but 1 had an objective immunotherapy response (97%).

### Discussion

The 2016 AE guidelines permit autoimmune causation assessment in subacute encephalopathy and are highly specific. Inclusion could be improved by incorporating AE-IgG–positive patients with isolated seizures or brainstem disorders. Some patients with atypical presentations but with findings supportive of autoimmunity may be immune therapy responsive.

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Certain neural autoantibodies have a very high specificity for autoimmune encephalitis (AE) and have led to an improved recognition of AE and related disorders in general.<sup>1</sup> However, many patients are seronegative (possibly as high as 50%), lending further emphasis to the importance of accurate clinical history, examination, and supportive paraclinical diagnostic tests (such as MRI, inflammatory CSF parameters, and EEG).<sup>2,3</sup> Guidelines to aid the prompt diagnosis of AE were published in 2016.<sup>4</sup> These provide a framework for the assessment of patients presenting with subacute onset altered mental status and short-term memory loss principally using clinical assessment, MRI, and CSF white cell count.<sup>4</sup> In that algorithmic assessment, to meet at least possible AE criteria, patients require subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status (altered level of consciousness, lethargy, or personality change) or psychiatric symptoms with at least 1 of new focal CNS findings, new-onset seizures, CSF pleocytosis, and supportive MRI. These tests are complemented by AE-specific IgG antibody testing, CSF IgG index and oligoclonal bands, EEG, and brain biopsy to further refine diagnostic certainty. Specificity is assured by the requirement for reasonable exclusion of other diagnoses and differing levels of diagnostic certainty (possible, probable, and definite). Discerning the characteristics and relative frequencies in the clinical practice of different AE disorder subcategories (possible, probable, definite, and seropositive or seronegative) and related encephalopathies not meeting at least possible AE criteria (e.g., those with primarily seizure disorders without encephalopathy, brainstem disorders without altered awareness, and atypical presentations) would be informative for clinical treatment decisions, epidemiologic studies, and clinical trial design.

In this study, we applied the AE guidelines to 538 adult patients diagnosed with diverse autoimmune encephalopathies within our practice (Autoimmune Neurology Clinic, Mayo Clinic, Rochester, MN).<sup>4</sup> The scope of this assessment did not include pure ataxias, stiff-person syndrome, or other pure movement disorders.<sup>5</sup>

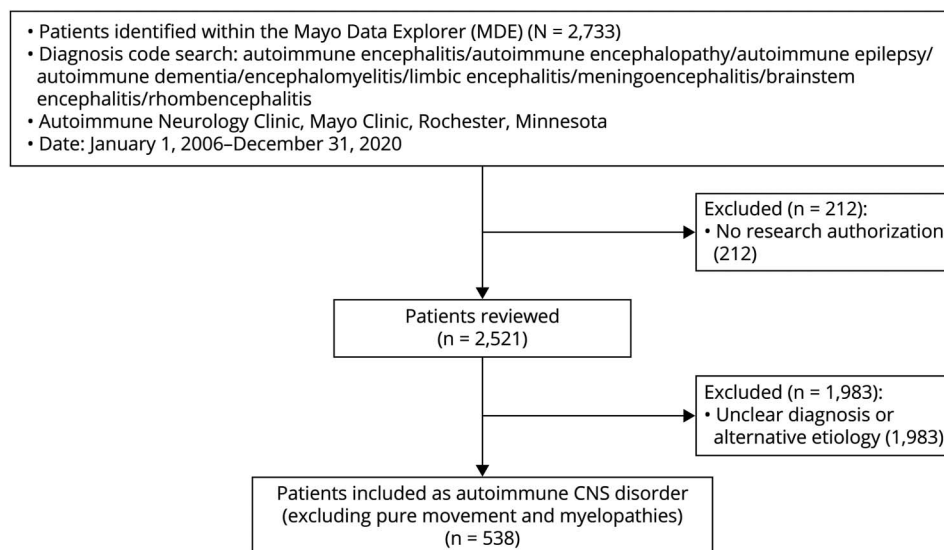
## Methods

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

This retrospective study was approved by the Mayo Clinic Institutional Review Board (IRB, 21-001297). Medical records of patients who consented to research review were included.

Initially surveyed medical records were from 2,733 adult patients evaluated clinically by one of the authors (January 1, 2006 until December 31, 2020) who had at least one of the following diagnoses recorded: encephalitis, encephalopathy, epilepsy, seizures, dementia, encephalomyelitis, limbic encephalitis, meningoencephalitis, brainstem encephalitis, rhombencephalitis, Bickerstaff encephalitis, Hashimoto encephalopathy, and its alternative moniker steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), Figure 1. Patients evaluated in the Autoimmune Neurology Clinic were either referred directly as outpatient or had been initially evaluated at the Mayo Clinic Hospital. Of those 2,733 patients, 212 lacking documented research authorization were excluded from further review. Of 2,521 charts reviewed, 1,983 patients were excluded from the study because they had one of the following: other nonautoimmune final diagnosis, uncertain diagnosis, isolated autoimmune movement disorder

**Figure 1** Study Inclusion Algorithm



(myoclonic disorder, cerebellar ataxia, chorea, or stiff-person syndrome), or autoimmune myelopathy or autoimmune neuropathy occurring in isolation.

The remaining 538 patients all had AE or related disorder diagnosis made by a Mayo Clinic neuroimmunologist ( $\geq 1$  of the coauthors) and had a reasonable exclusion of other nonimmune-mediated diagnoses.<sup>4</sup> The medical records for those 538 patients were further reviewed. Clinical and testing data were abstracted from the medical records and documented in a password-protected database. Data were evaluated for each patient to determine whether at least “possible AE” criteria were met (Table 1). For those meeting at least possible AE criteria, clinical, MRI, CSF, brain biopsy, and autoantibody data were reviewed to determine whether criteria were met for other AE subgroups (definite, seronegative

but probable, Hashimoto encephalopathy/SREAT, acute disseminated encephalomyelitis [ADEM], and Bickerstaff brainstem encephalitis). The same data points were also recorded for the remaining patients not meeting possible criteria. In addition, for those cases, antibody status, coexisting autoimmune diseases, immune therapies used, and physician-observed responses were recorded.

All 538 patients had undergone evaluation in the Mayo Clinic Neuroimmunology Laboratory for neural antibodies pertinent to AE in both the serum and CSF (486), the CSF only (1), or the serum only (51). AE-specific neural IgG antibodies included in our analyses included those antibodies already described during publication of the 2016 AE Guidelines (e.g., n-methyl-D-aspartate [NMDA] receptor [R]-IgG [in the CSF]; high-titer [ $\geq 20$  nmol/L, equivalent to

**Table 1** Autoimmune Encephalitis Diagnostic Guidelines

Criteria	Main AE syndrome	AE-typical supportive features						AE-specific Ab	Exclusion other causes
		New focal CNS finding	New seizures	CSF	MRI	EEG	Brain biopsy		
<b>Possible</b>	Subacute onset $\leq 3$ mo of memory deficits/AMS/psych	Req <sup>a</sup>	Req <sup>a</sup>	Req-Pleo <sup>a</sup>	Req <sup>a</sup>				Req
<b>Those meeting “Possible” criteria can then be assessed for further categorization, below</b>									
<b>Definite LE</b>	Subacute onset $\leq 3$ mo of memory deficits/AMS/psych suggestive of limbic system disorder			Req-Pleo <sup>a</sup>	Req-LE	Req-Temp <sup>a</sup>		Opt	Req
<b>Probable Anti-NMDA-R</b>	$\geq 4$ of 6 of cognitive or psych, speech dysfunction, movement disorder, decreased consciousness, dysautonomia, or hypoventilation			Req-Pleo/OCB <sup>a</sup>		Req-E <sup>a</sup>		NMDA-R	Req
<b>Definite, other</b>	Meet at least possible criteria. Diverse disorders (e.g., LGI1 encephalitis, CASPR2 encephalitis, and GABA <sub>A</sub> -R encephalitis)							Req	Req
<b>Definite ADEM</b>	First multifocal CNS event, inflammatory, demyelinating cause, & encephalopathy not explained by fever & no new findings after 3 mo				Req-AD				Req
<b>Bickerstaff's BE</b>	Subacute onset decreased consciousness, bilateral external ophthalmoplegia & ataxia							GQ1B	Req
<b>Hashimoto</b>	AE with seizures, myoclonus, hallucinations or stroke-like episodes & subclinical or mild thyroid disease				Req-N			ND, Req-Thyr	Req
<b>Probable</b>	Subacute onset $\leq 3$ mo of memory deficits/AMS/psych w/o other well-defined AE syndrome			Req-Pleo/OCB/IgG <sup>b</sup>	Req <sup>b</sup>		Req <sup>b</sup>	ND	Req

Abbreviations: AD = typical ADEM MRI findings (diffusely poorly demarcated, large [ $>1-2$  cm] lesions predominantly involving the cerebral white matter; T1-hypointense lesions in the white matter in rare cases; deep gray matter abnormalities [e.g., thalamus or basal ganglia] can be present, resolving); E = focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush; GQ1B = anti-GQ1B optional for diagnosis if bilateral external ophthalmoplegia not present or ataxia not assessable; IgG<sub>I</sub> = elevated CSF IgG index; LE = bilateral abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes; N = normal MRI; ND = neuronal Ab not detected in the serum or CSF; NMDA-R = NMDA-R Ab optional for diagnosis (definite diagnosis can be made with Ab positivity in the presence of  $\geq 1$  of the 6 major groups of symptoms); OCB = abnormal CSF oligoclonal band numbers; Opt = optional (if present, only 1 of MRI or supportive CSF or EEG findings required); Pleo = pleocytosis (elevated white cell count) in the CSF; psych = psychiatric symptoms; Req = required; Temp = EEG with epileptic or slow-wave activity involving the temporal lobes; Thyr = thyroglobulin or thyroid peroxidase antibodies.

<sup>a</sup>  $\geq 1$  of supportive features required.

<sup>b</sup>  $\geq 2$  of supportive features required.

>10,000 IU/mL] glutamic acid decarboxylase 65 kDa isoform [GAD65] antibody [in the serum or any titer detected in the CSF]; and leucine-rich glioma-inactivated [LGI1] antibody, contactin-associated protein 2 [CASPR2], or antineuronal nuclear antibody type 1 [ANNA-1, anti-Hu] detected in any specimen type).<sup>4</sup> We excluded those antibodies with a limited specificity for AE (e.g., non-LGI-1/CASPR2 voltage-gated potassium channel antibodies, calcium channel antibodies, low-positive GAD65 antibody, and NMDA-R-IgG detected in the serum only).<sup>4,6-8</sup> In addition, we included antibodies with high disease specificity reported since 2016 (glial fibrillary acidic protein [GFAP] and neuronal intermediate filament [NIF] IgGs detected in the CSF) and adenylate kinase 5 antibody.<sup>9-11</sup> Because we included cases with brainstem encephalitis in our analyses, we also included ANNA-2 (anti-Ri), immune globulin-like family member 5 (IgLON5), and kelch-like protein 11 (KLHL11) IgGs as AE-specific biomarkers.<sup>12-14</sup> Positivity in either the serum or CSF was acceptable except for NMDA-R, GFAP, and NIF IgGs, where CSF positivity was required. Paraneoplastic associations where pertinent were as previously reported (e.g., ANNA-1 and small cell carcinoma).<sup>15</sup> Intergroup nonparametric categorical data were compared using the Fisher exact test ( $p < 0.05$  was considered significant).

### Data Availability

Anonymized data used for this study are available on request.

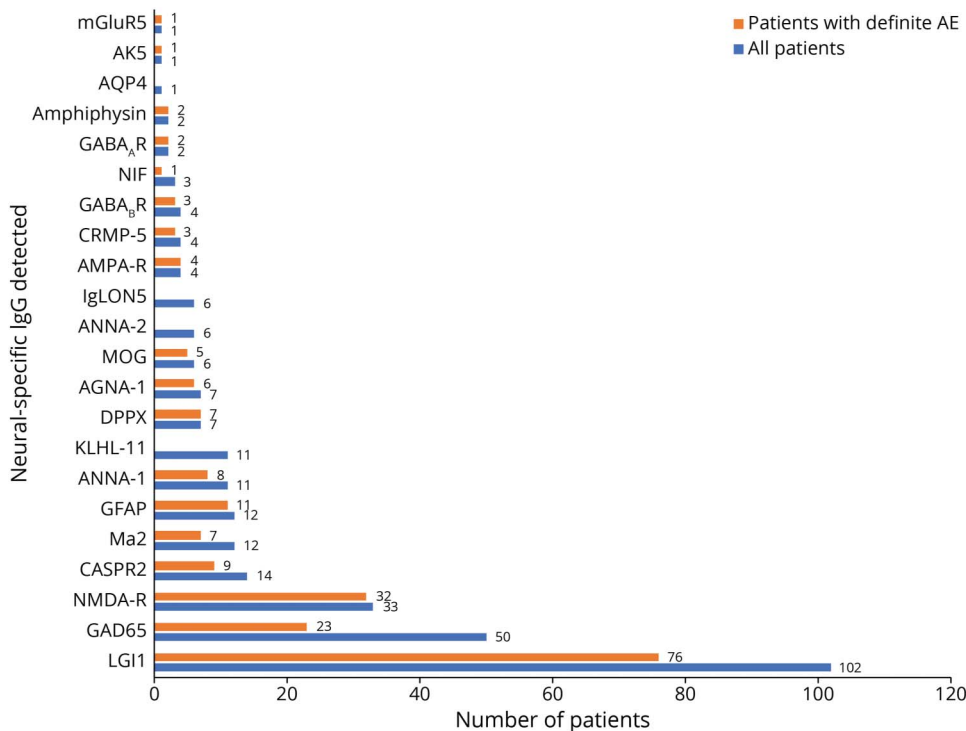
## Results

Of 538 included patients who were evaluated in our Auto-immune Neurology Clinic, 288 were male (52%). The median symptom onset age was 55 years (range, 11–97 years). Sixteen patients had symptom onset as children but were assessed in our clinic for AE diagnosis after turning 18 years. Two hundred ninety-one patients had  $\geq 1$  AE-specific IgG detected (54%), and 247 were seronegative (Figure 2). Of the 247 seronegative cases, 12 had an unclassified neural-restricted IgG antibody detected by tissue IFA (5%). These were detected in the CSF only where the serum showed negative results (9), in both the serum and CSF (2), and in the serum only where the CSF was not submitted for testing (1). The distribution of diagnoses of the 538 patients based on the 2016 AE criteria is summarized in Figure 3.

### Two-Thirds of Patients Fulfilled at Least Possible AE Criteria, Most of Whom Had Definite AE

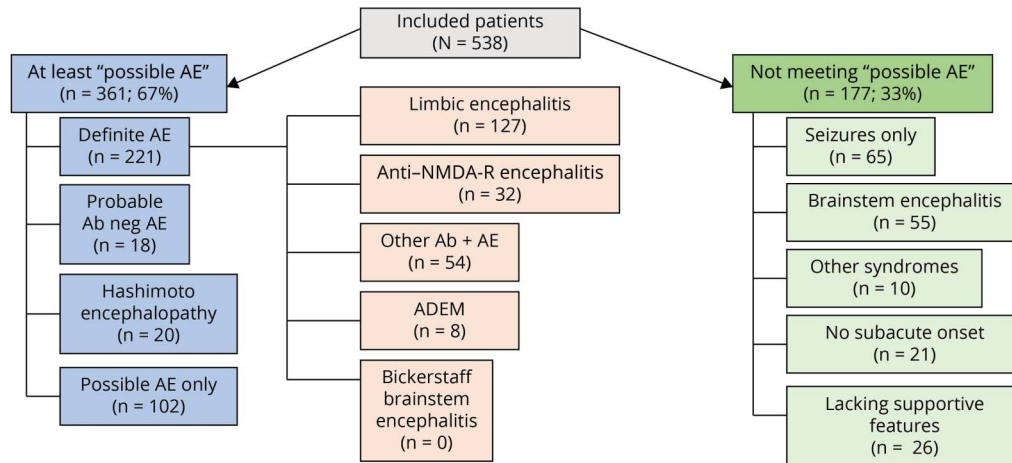
Of 538 patients, 361 (67%) met at least possible criteria, having all 3 of subacute onset, memory deficits, altered mental status or psychiatric symptoms, and had at least 1 supportive feature (new focal objective CNS finding, 285 [79%]; new-onset seizures, 283 [78%]; supportive MRI findings, 251 [70%], or CSF pleocytosis, 160 [44%]). Of the 361 patients, 221 (61%) had definite AE, 18 (5%) had probable AE, and 102 (28%) had possible AE not otherwise

**Figure 2** Autoantibody Findings Among All 538 Patients and 221 Cases With Definite AE



Ab = antibody; AGNA = antiglial/neuronal nuclear antibody; AK5 = adenylate kinase 5; AMPA =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Amphi = amphiphysin; ANNA = antineuronal nuclear antibody; AQP4 = aquaporin-4; CASPR = contactin-associated protein; CRMP = collapsin-response mediator protein; DPPX = dipeptidyl peptidase; GABA = gamma amino butyric acid; GAD65 = glutamic acid decarboxylase 65 kDa isoform; GFAP = glial fibrillary acidic protein; IgLON = immunoglobulin-like cell adhesion molecule; KLHL = kelch-like protein; LGI1 = leucine-rich glioma-inactivated 1; mGluR5 = metabotropic glutamate receptor-5; MOG = myelin oligodendrocyte glycoprotein; NIF = neuronal intermediate filaments; NMDA = n-methyl-D-aspartate; R = receptor.

**Figure 3** Diagnostic Categories for 538 Patients After Application of 2016 Autoimmune Encephalitis Criteria



Ab = antibody; ADEM = acute disseminated encephalomyelitis; AE = autoimmune encephalitis; NMDA-R = n-methyl-D-aspartate receptor.

categorized. Twenty patients (6%) met Hashimoto encephalopathy criteria, Table 2.

### Patients With Definite AE Were Usually AE-Specific IgG Positive (87%)

The 221 patients with definite AE had limbic encephalitis (N = 127, 57%), had anti-NMDA-R encephalitis (N = 32, 15%), had ADEM (N = 8, 4%), or were classified as “other” (N = 54, 24%), Figure 3. Of 221 cases with definite AE, 193 were neural antibody positive (87%). Among seropositive patients, 18 different neural antibodies were detected in the serum, the CSF, or both, the 3 most common being leucine-rich glioma-inactivated protein 1 (LGII; 76, 34%), NMDA-R (32, 16%), and high-titer GAD65 (23, 12%), Figure 2, eTable 1, [links.lww.com/CPJ/A412](https://links.lww.com/CPJ/A412). Coexisting antibodies in 8 patients were in 3 with anti-NMDA-R encephalitis with either GFAP-IgG (2 patients) or myelin oligodendrocyte glycoprotein (MOG)-IgG (1 patient) coexisting, all with typical anti-NMDA-R encephalitis; 4 with limbic encephalitis (with 1 each of gamma amino butyric acid [GABA]<sub>A</sub>R and GAD65; LGII and contactin-associated protein-2 [CASPR2]; ANNA-1, amphiphysin and GABA<sub>B</sub>R, or antiglial/neuronal nuclear antibody type 1 [AGNA-1, also known as SOX-1]; and GABA<sub>B</sub>R); and 1 with typical GABA<sub>A</sub>R encephalitis and coexisting GAD65 antibody.

Of 221 definite cases, 141 (60%) required antibody positivity to fulfill definite criteria (Figure 3, eTable 1, [links.lww.com/CPJ/A412](https://links.lww.com/CPJ/A412)). Subgroups of patients requiring antibody positivity to meet the definite criteria were as follows: limbic encephalitis, 64/127 (50%, including 56 of 76 cases with LGII, 74%); anti-NMDA-R encephalitis, 23/32 (72%), ADEM, 1/8 (13%, MOG-IgG positive), and all 54 “other” cases fulfilling criteria based on meeting possible criteria and being AE-specific antibody positive, eTable 1, [links.lww.com/CPJ/A412](https://links.lww.com/CPJ/A412). Among 127 cases that met definite limbic

encephalitis criteria, 11 (9%) did not meet criteria in the absence of antibody positivity because T2 MRI changes were unilateral only (LGII, 5; GAD65, 4; ANNA-1, and Ma2, 1 each), Figure 4. The 54 “other” patients not meeting definite limbic encephalitic criteria but still had antibody positivity to meet definite AE criteria had either: nonlimbic syndromes (16 patients [30%], with autoimmune GFAP astrocytopathy [9, with radiologic features of meningoencephalitis], dipeptidyl peptidase-6 [DPPX] autoimmunity [6, with multifocal encephalomyelitis, with gastrointestinal symptoms and weight loss], and GABA<sub>A</sub>R encephalitis [1, encephalopathy with extratemporal seizures]) or lack of sufficient supportive findings despite having a typical limbic syndrome (38, 70%). While those 38 patients without sufficient supportive findings had temporal lobe EEG changes in most cases (33, 89%), they all lacked supportive CSF and MRI findings (pleocytosis and bilateral limbic encephalitic changes). Of note, 6 of those patients did have unilateral T2 changes (5 cases with LGII and a single case with metabotropic glutamate receptor-5 [mGluR5]).

No cases of Bickerstaff brainstem encephalitis were encountered. A wider search of the Mayo medical records beyond the scope of our Autoimmune Neurology group (2006–2020) yielded 1 case with Bickerstaff encephalitis case evaluated in our department 2 years after hospitalization elsewhere (ganglioside GQ1B antibody positive). Twenty patients met 2016 criteria for Hashimoto encephalopathy (Table 2).

### Patients Meeting Probable Seronegative or Possible AE Criteria Had Diverse Findings

All 18 patients with probable but seronegative AE had both MRI and CSF findings supportive of the diagnosis, 5 of whom also underwent brain biopsy (all 5 had supportive histologic evidence of inflammatory infiltrates, Table 2). The other 102

**Table 2** Characteristics of All Patients With Possible, Probable, and Definite Autoimmune Encephalitis and Those Not Meeting at Least Possible Criteria

	Subacute onset, AMS/memory loss ± psychiatric symptoms, N (%)	New focal CNS findings, N (%)	New-onset seizures, N (%)	Supportive CSF, N (%)	Supportive MRI, N (%)	EEG findings	Supportive brain biopsy, N (%)	Neural Ab positive, N (%)
<b>Definite AE, N = 221</b>	221 (100)	124 (56)	154 (69)	74 (33) <sup>a</sup> Pleo 74 (33) OCB, 50 (23) IgG, 24 (11)	136 (62)	Epileptiform d/cs, 102 Slowing only, 56 Normal, 43 NA, 20	1 (of 3 performed), NR	194 (88%, 4 <sup>c</sup> )
<b>Ab negative but probable AE, N = 18</b>	18 (100)	12 (67) NR	7 (38) NR	17 (94) <sup>b</sup> Pleo, 14 (78) OCB, 5 (28) IgG, 5 (28)	17 (94)	Epileptiform d/cs, 3 Slowing only, 5 Normal, 5 NA, 5	5 (of 5 performed)	0 (2 <sup>c</sup> )
<b>Hashimoto encephalopathy, N = 20</b>	20(100)	13 (65) NR	12 (60) NR	4 (20) NR Pleo, 4 (20) OCB, 1 (5) IgG, 0	20 (100) N	Epileptiform d/cs, 5 Slowing only, 6 Normal, 6 NA, 3	O, NR	0
<b>Possible AE without further category, N = 102</b>	102 (100)	56 (55)	39 (38)	31 (30) <sup>a</sup> Pleo 31 (30) OCB, 9 (9) IgG, 5 (5)	36 (35)	Epileptiform d/cs, 36 Slowing only, 26 Normal, 27 NA, 13	1 (of 4 performed), NR	0 (3 <sup>c</sup> )
<b>Not meeting possible criteria N = 177</b>	156 (88)	71 (40)	65 (37)	52 (29) <sup>b</sup> Pleo 37 (21) OCB, 35 (20) IgG, 16 (9)	54 (31)	Epileptiform d/cs, 44 Slowing only, 33 Normal, 40 NA, 60	2 (of 2 performed)	98 (55), 3 <sup>c</sup>

Abbreviations: Ab = antibody; AE = autoimmune encephalitis; AMS = altered mental status; D/Cs = discharges; N = normal or nonspecific appearing MRI supportive of Hashimoto encephalopathy diagnosis; NA = not available; NR = not relevant to the criteria subset.

<sup>a</sup> Only CSF pleocytosis (Pleo; normal, ≤5/μL) considered supportive.

<sup>b</sup> CSF pleocytosis (Pleo), CSF oligoclonal bands (OCB, normal, <2), or elevated IgG index (IgG, normal, ≤0.85) or both considered supportive.

<sup>c</sup> Patients had unclassified antibodies detected.

patients met possible criteria only (Table 2), one of whom did not meet definite limbic encephalitis criteria owing to unilateral rather than bilateral hippocampal T2 hyperintensity. Inflammatory-appearing MRI findings were diverse among the probable and possible group patients (examples shown in Figure 4).

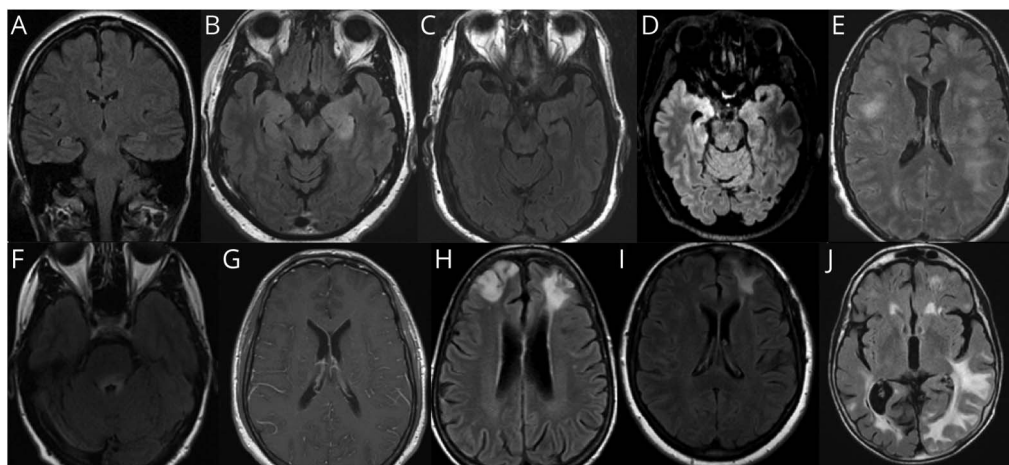
### Two-Thirds of Patients Not Meeting at Least Possible AE Criteria Had Isolated Seizures or Brainstem Encephalitis

Of the 177 patients (33% of 538) evaluated and diagnosed with autoimmune encephalopathy who did not meet at least 2016 possible AE criteria (Tables 2 and 3, Figure 3), 120 (68%) had either seizures only (65, 12% of all patients) or brainstem encephalitis without supratentorial findings (55, 10% of all patients), and 83 cases were neural antibody positive (69%, Table 3). Patients with brainstem encephalitis had diverse combinations of eye movement disorders (35), ataxic (28) or postural (32) difficulties, vestibulocochlear symptoms (18, including deafness in 5), upper motor neuron signs (13), dysarthria (13), dysphagia (9), other cranial neuropathies (7), and tremulousness (5). Seven of 11 patients with KLHL-11-IgG positivity had vestibulocochlear symptoms. One patient had AQP4-IgG positivity and

isolated (radiologically inflammatory appearing) brainstem encephalitis, thus meeting NMO diagnostic criteria.<sup>16</sup> Twenty-one patients without pleocytosis in the CSF had oligoclonal bands (20) or an elevated IgG index (8) detected, 4 of whom did not meet possible criteria for lack of supportive findings. Epileptiform EEG abnormalities in the “seizure-only” patients (captured in 36 of 65, 55%) were temporal (28), extratemporal (4), or both (4).

### The Remaining 57 Patients Did Not Meet at Least Possible AE Criteria for Diverse Reasons

The remaining 57 of 177 patients (32%) lacked supportive clinical, radiologic, or CSF findings (26), had insidious or initially episodic onset of otherwise typical disorders (21), or atypical multifocal syndromes with cognitive symptoms in the absence of memory deficits or altered mental status (10), Table 3. Characteristic features supporting an autoimmune diagnosis in the 57 patients were diverse. These were typical neurocognitive syndrome by AE criteria (47, 82%), subacute onset (36, 63%), new focal CNS findings (15, 26%), inflammatory CSF abnormalities (15, 26%; 1 or more of CSF-exclusive oligoclonal bands [11], pleocytosis [9], or an elevated IgG index [3]), AE-specific antibodies (15, 26%: CASPR2, 3; GAD65, 2; LGI1, 2; NIF, 2; GFAP, NMDA-R,



Images are T2 axial FLAIR, except A (T2 coronal FLAIR) and G (T1 axial postgadolinium). (A) Normal appearing hippocampal formations in a patient with anti-NMDA-receptor encephalitis. (B) Bilateral hyperintensity of hippocampal formations in a patient with LGI1 encephalitis. (C) Subtle left hippocampal hyperintensity in a patient with LGI1 encephalitis. (D) Prominent right amygdalar hyperintensity in a patient with anti-Ma2 encephalitis. (E) Multifocal white matter lesions with ill-defined borders in a patient with MOG antibody-associated disease and an ADEM attack. (F) Peri-IVth ventricular hyperintensity in a patient with aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder with brainstem encephalitis; (G) Periventricular leptomeningeal enhancement in a patient with autoimmune GFAP astrocytopathy. (H) Bifrontal lobar hyperintensities in a patient with GABA<sub>A</sub> receptor encephalitis. (I) Left frontal hyperintensity in a patient with possible autoimmune encephalitis. (J) Diffuse T2 signal abnormalities in a patient with probable autoimmune encephalitis. ADEM = acute disseminated encephalomyelitis; FLAIR = fluid-attenuated inversion recovery; GABA = gamma amino butyric acid; GFAP = glial fibrillary acidic protein; LGI1 = leucine-rich glioma-inactivated 1; MOG = myelin oligodendrocyte glycoprotein; NMDA-R = n-methyl-D-aspartate receptor.

collapsin-response mediator protein-5, Ma2, MOG, and IgLON5, 1 each), inflammatory MRI findings (13), seizures (5), and supportive brain biopsy findings (2). In addition, physician-reported immune therapy responses were recorded in 52 of 57 patients (91%). One of the 57 patients had 6 of these 8 abovementioned characteristics (2%), 6 had 5 (11%), 14 had 4 (26%), 32 had 3 (56%), and 3 had 2 (5%). When compared with the 102 patients meeting 2016 possible AE criteria only, the 57 patients were as likely to have coexisting seizures (39/102 v 14/57,  $p = 0.083$ ), supportive MRI findings (36/102 v 13/57,  $p = 0.150$ ), or CSF pleocytosis (31/102 v 9/57,  $p = 0.057$ ) but were less likely to have new focal CNS findings (56/102 v 14/57,  $p = 0.004$ ).

### Coexisting Autoimmunity and Treatment Responses Were Diagnostically Useful in 8% of the Cohort

Among 42 (of the 57) patients who were neural IgG negative, other evidence of diverse organ-specific autoimmunity was encountered in 31 (74%), eTable 2, [links.lww.com/CPJ/A412](https://links.lww.com/CPJ/A412). Twenty-one had  $\geq 1$  coexisting autoimmune disease (50%, autoimmune thyroid disease, 14; B<sub>12</sub> deficiency, 4; type 1 diabetes, 2; celiac disease, 2; and 1 each of autoimmune hemolytic anemia, immune thrombocytopenic purpura, sclerosing cholangitis, ulcerative colitis, systemic lupus erythematosus, rheumatoid arthritis, leukocytoclastic vasculitis, and preexisting Lambert-Eaton syndrome) and 23 had  $\geq 1$  non-neurological disease-specific antibodies detected (55%, thyroid, 17 [thyroid peroxidase, 16; thyroglobulin, 1]; low-positive [ $\leq 20$  nmol/L] GAD65, 5; p-ANCA, 1; phospholipid antibody, 1), and 1 had an unclassified neural antibody detected in the CSF. Twenty-

five of 42 patients had clinical or serologic evidence of thyroid autoimmunity (60%). All but 1 of 42 patients had objective improvements in neurologic examination reported by the treating clinician (97%), supported by improvements on formal bedside cognitive or neuropsychometric testing (14), EEG (7), MRI (4), or PET-CT (1).

Among the 3 most common seropositive subgroups in the entire cohort of 538 patients (LGI1, GAD65, and NMDA-R), 54 of 160 patients did not meet at least possible 2016 criteria (34%): LGI1 26/76 patients (34%, seizures only, 24; and lack of supportive features, 2); GAD65 27/51 patients (53%, seizures only 22, brainstem encephalitis, 3, lack of subacute onset, 2); NMDA-R 1/33 patients (3%, lack of supportive features), Table 3.

### Psychiatric Symptom-Predominant Phenotypes Were Uncommon and Not Typical of Primary Psychiatric Disorders

Thirteen of 538 patients presented with predominant or exclusive psychiatric symptoms (2.5%). They had subacute symptom onset of multimodal neuropsychiatric presentations consisting of altered mental status (all 13), behavior or personality change (10), paranoid delusions (5), auditory and/or visual hallucinations (4), agitation (3), catatonia (3), and suicidal ideation (2). Nine of 13 (69%) had focal objective CNS findings (abnormal cognitive examination [8], aphasia [1], hypomimia [1], and apraxia with hyperreflexia [1]), 4 had supportive MRI findings, and 3 had supportive CSF pleocytosis (an additional 2 had CSF-exclusive oligoclonal bands). All but 1 of 13 met at least possible AE criteria.

**Table 3** 177 Patients Who Did Not Meet Possible Autoimmune Encephalitis Criteria: Reasons for Not Meeting Criteria and Characteristics Leading to Autoimmune Diagnoses

Rational for not meeting possible AE criteria	Autoimmune diagnostic characteristics				
	Focal CNS findings, N (%)	Abs detected, N (%)	Seizures, N (%)	Inflammatory-appearing MRI, N (%)	Inflammatory CSF, N (%)
<b>Seizures only</b> N = 65	17 (27)	50 (77) LGI1, 24, GAD65, 22 CASPR2, 2 Ma2, 1 GABA <sub>B</sub> R, 1 Seronegative, 15 (unclassified Ab, 1)	65 (100)	21 (32)	10 (14) Pleo, 5 OCB, 5 IgG1, 1
<b>BE without altered consciousness</b> N = 55	55 (100)	33 (60) KLHL11, 11 ANNA-2 (anti-Ri), 6 IgLON5, 5 GAD65, 3 Ma2, 3 ANNA-1 (anti-Hu), 3 AGNA1 (SOX-1), 1 AQP4, 1 Seronegative, 22 (unclassified Ab, 1)	1 (2)	20 (36)	27 (49) Pleo, 15 OCB, 19 IgG1, 12
<b>Other atypical syndromes</b> N = 10	5 (50)	3 (33) CRMP-5, 1 GFAP, 1 NIF, 1 Seronegative, 7 (unclassified Ab, 1)	2 (20)	7 (70)	6 (60) Pleo, 5 OCB, 6 IgG1, 2
<b>Lacking subacute onset</b> N = 21	10 (48)	7 (33) GAD65, 2 IgLON5, 1 Ma2, 1 NIF, 1 NMDA-R, 1 MOG, 1 Seronegative, 14	3 (14)	6 (29)	7 (33) Pleo, 4 OCB, 3 IgG1, 1
<b>Lacking supportive features</b> N = 26	0	5 (19) CASPR2, 3 LGI1, 2 Seronegative, 21	0	0	2 (8) OCB, 2

Abbreviations: Ab = antibody; AGNA = antiglial/neuronal nuclear antibody; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Amphi = amphiphysin; ANNA = antineuronal nuclear antibody; AQP4 = aquaporin-4; BE = brainstem encephalitis; CASPR = contactin-associated protein; CRMP = collapsin-response mediator protein; DPPX = dipeptidyl peptidase; GABA = gamma amino butyric acid; GAD65 = glutamic acid decarboxylase 65 kDa isoform; GFAP = glial fibrillary acidic protein; IgG1 = IgG index; IgLON = immunoglobulin-like cell adhesion molecule; KLHL = kelch-like protein; LGI1 = leucine-rich glioma-inactivated 1; MOG = myelin oligodendrocyte glycoprotein; NIF = neuronal intermediate filament antibodies, NF-H-IgG+; MOG = myelin oligodendrocyte glycoprotein; NMDA = n-methyl-D-aspartate; Pleo = pleocytosis; OCB = oligoclonal bands; R = receptor; SOX1 = SRY-box transcription factor 1.

Diagnoses were anti-NMDA-R encephalitis, 6 (all were NMDA-R antibody positive in the CSF); anti-DPPX encephalitis, 1, and Hashimoto encephalopathy/SREAT, 1. Of the 5 remaining patients (seronegative), 4 met only possible criteria, and 1 met definite limbic encephalitis criteria. Immune therapy responses were evident in all 13.

## Discussion

We applied the 2016 AE guidelines to our patients diagnosed with diverse autoimmune encephalopathies encountered in our clinical practice to understand their utility in assisting diagnostic decision-making.<sup>4</sup> We found two-thirds of our patients diagnosed with an autoimmune brain disease (excluding ataxias and other movement disorders) met at least possible criteria. The guidelines permit structured assessment of patients with

subacute-onset brain disorders using clinical and paraclinical data points to determine differing levels of diagnostic certainty (probable, definite, or possible, not otherwise specified). These are helpful in delineating the key diagnostic features for clinical practice and have also been used in the design of clinical trials and other research studies.<sup>3,17</sup> Although our study was not designed to address the specificity of criteria among a control cohort, in our clinical experience, the definite AE criteria are highly specific, which is assured by the “reasonable exclusion of other diagnoses” requirement. In addition, we did not find alternative diagnoses among the cases where there was less certainty (possible, probable, or not meeting 2016 criteria). A longitudinal data collection to assess for any changes in diagnoses over time will be conducted in the future.

These 2016 AE criteria focused on being as specific as possible and were moderately sensitive in our patients. We



respect the work conducted by others to date and acknowledge the impossibility of capturing all patients with disparate autoimmune encephalopathies using a single set of criteria without losing specificity. Some modification of the criteria could improve inclusion of AE-specific IgG-positive patients with seizure-only presentations, brainstem encephalitis, and perhaps some atypical presentations. This would ensure broader inclusion of affected patients in relation to epidemiologic studies, clinical trials, treatment guidelines, healthcare policies, and insurance rules developed in the future.

From our experience, the most common presentation beyond those specified in the AE guidelines was isolated seizures (12%), similar to the frequency previously reported for isolated seizures in general for LGI1 encephalitis (13%) and anti-NMDA-receptor encephalitis (12%).<sup>18,19</sup> In our experience, LGI1 encephalitis presents with seizures in the absence of the full clinical picture of limbic encephalitis in one-third of cases (and thus would not be included in AE criteria). By contrast, the AE guidelines were sufficiently sensitive to detect anti-NMDA-R encephalitis except in 1 patient, who lacked subacute onset. The next most common category of patients not meeting criteria were those with brainstem encephalitis (10%), with neither altered awareness nor bilateral external ophthalmoplegia typical of Bickerstaff encephalitis, which was included in the 2016 guidelines.<sup>4,20</sup> Despite being included in the diagnostic criteria, we never encountered a patient with Bickerstaff encephalitis in our practice, and only encountered 1 within our institution who met AE diagnostic guidelines during the study epoch. In our experience, brainstem encephalitis most commonly presents with subacute onset of cerebellar ataxic signs, postural instability, and symptomatic eye movement abnormalities. One or more of deafness, vertigo, speech and swallow difficulties, jaw dystonia, upper motor neuron signs, spasms, bowel or bladder dysfunction, myoclonus, or tremor were other accompaniments. Vestibulocochlear symptoms are frequent in KLHL11 autoimmunity.<sup>21</sup>

Though highly specific, the 2016 guidelines were not designed to capture the heterogeneous group of patients (10% of our entire cohort) who did not meet possible AE criteria yet had a constellation of features suspicious for an autoimmune cause and who responded to immune therapy in almost all cases. One of the defining features of the 2016 AE criteria (subacute onset, typical neurocognitive syndrome, and sufficient supportive features) was absent in those 57 patients, yet suspicion for an autoimmune cause persisted. For 15 (25%) of those patients, autoimmune diagnoses were straightforward to confirm because AE-specific IgG testing in the serum or CSF was positive. However, for the remaining 42 seronegative patients, the diagnoses were less certain and illustrative of the importance of continued biomarker discovery for seronegative autoimmune neurologic disorders. Additional features we have found helpful over the years include a preexisting personal history of autoimmune disease

(most commonly thyroid disease), CSF markers beyond pleocytosis (elevated IgG index, IgG synthesis rate, and oligoclonal bands), research-based testing for novel unclassified neural IgGs, and occasionally brain biopsy.<sup>22</sup> Furthermore, all but 1 of those 42 patients had a physician-observed response to immune therapy. Although ideal to ascertain an autoimmune diagnosis before treatment, our experience and these data portend a lack of feasibility in some cases.<sup>23</sup> Where there is uncertainty, before an immune therapy trial, we emphasize the importance of reasonable exclusion of other reversible disorders, such as neoplastic, infectious, toxic, and metabolic disorders, so as to leave 2 main possibilities remaining: an immune-mediated disorder or a neurodegenerative diagnosis with limited treatment options. Patients should be followed up expeditiously to determine whether there is an objective response to immune therapy and treatment promptly tapered and discontinued where there is none.

Some of our patients met criteria for Hashimoto encephalopathy (2016) while others (among our 42 seronegative cases not meeting possible criteria) met the less stringent SREAT criteria.<sup>24</sup> Either way, the significance of thyroid autoantibodies (and other non-neural IgGs such as low-positive GAD65 antibody) should be interpreted with caution because they can be encountered in healthy people also. Three-quarters of patients referred to our practice for Hashimoto encephalopathy/SREAT received a final non-autoimmune diagnosis.<sup>25</sup> In general, in this study, we diagnosed autoimmune encephalopathy in 1 in 5 of all patients assessed.

From a practical perspective, it would be difficult to capture all diverse patients from our practice we have described in this study in diagnostic criteria without losing specificity. Nonetheless, the sensitivity for possible AE could be improved by including some well-recognized seropositive “seizure-only” presentations, as previously described.<sup>26</sup> A recent review of conceptual definitions suggested the terms “acute symptomatic seizures secondary to AE” to refer to seizures occurring in the setting of the active phase of immune-mediated encephalitis and provided a detailed summary of typical features of new-onset seizures in that context.<sup>27</sup> The 2016 AE guidelines could be modified to include isolated new-onset, frequent, focal seizures among the clinical presentations, while retaining the other supportive criteria and requirement to exclude competing diagnoses.<sup>27</sup> Similarly, a category could be added to current AE guidelines to include brainstem encephalitis, especially if seropositive for relevant neural autoantibodies, though the presentations are sufficiently diverse, distinct, and nascent in their recognition, that development of a separate brainstem-specific set of criteria could also be considered.<sup>28,29</sup>

Similar to our previous hospital-based experience, and the experience of others, psychiatric symptom-predominant autoimmune encephalopathies were distinct in presentation

from primary psychiatric disorders. Our patients had multimodal psychiatric presentations, usually admixed with neurocognitive signs.<sup>30,31</sup> In addition, those patients almost always had supportive findings and met AE diagnostic criteria. Therefore, a separate category of “autoimmune psychiatric” diagnoses seems unnecessary.<sup>32</sup> Similarly, autoimmune dementia, rather than being a separate diagnostic category, serves as “aide memoire” to cases of AE where rapidly progressive cognitive decline, without delirium, might mimic CJD or rapidly progressive Alzheimer disease or diffuse Lewy body disease.<sup>23</sup> The most challenging clinical presentations in our practice from a diagnostic standpoint include the 10% of patients with 1 of 3 central features atypical: nonsubacute onset (typically insidious with fluctuations), those with atypical symptomatology (such as admixed vague cognitive symptoms, language difficulties, and motor symptoms, where altered mental status and memory loss are not apparent), and those with a dearth of supportive clinical and paraclinical test findings. Nonetheless, those patients met 2 of the 3 central features, and if were AE-specific Ab negative, three-quarters had other clues supporting autoimmunity. Though not readily addressable in diagnostic criteria, in general within our practice, those patients would be diagnosed with possible autoimmune encephalopathy initially, and a likely diagnosis subsequently, if an objective immune therapy response occurred. We have found 1 or more of “before and after” MRI, EEG, and neuropsychometric testing to be of assistance in documenting treatment responses.

Limitations of our study include the potential for referral bias, favoring patients with unusual presentations not meeting AE criteria, given our tertiary outpatient subspecialty practice. In addition, our institution’s emphasis on US national ambulatory practice likely influenced LGI1 encephalitis being more common than anti-NMDA-R encephalitis. While we did encounter occasional patients without subacute symptom onset, it is also possible that some of those may have been artifacts of patient and family recall or documentation. In addition, antibody diagnostic evaluations were incremental in their sensitivity over time as new AE-specific IgGs were characterized. The largest AE subgroup was limbic encephalitis, 50% of whom required AE-specific IgG positivity to fulfill definite criteria, emphasizing the importance of antibody biomarkers in clinical practice.<sup>1</sup> Although patients with occasional limbic encephalitis in our series had unilateral limbic MRI changes, only 1 seronegative patient with possible AE did not fulfill limbic encephalitis criteria based on not having bilateral findings, and glioma should also be considered in these cases.<sup>33</sup>

In summary, for patients with a subacute onset cerebral syndrome, key details from the clinical history and examination, CSF, MRI findings and EEG, and utilization of the 2016 AE guidelines criteria assist in assessing the likelihood of an autoimmune cause. Antibody testing assists in confirming the diagnosis and may provide guidance for cancer evaluation in those with identification of a high-risk paraneoplastic antibody. In our view, it is also important to have a

low threshold for EEG, MRI, CSF, and serum/CSF antibody testing in a patient with an “outlier” clinical presentation in whom an alternative diagnosis is not immediately apparent and to consider an immune therapy trial. Future iterations of AE guidelines could capture more patients, particularly seropositive patients with isolated seizures and brainstem encephalitis. This would ensure optimized estimation of the epidemiologic burden of autoimmune encephalopathies and inform clinical trial design.

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