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Seizure Semiology in Antibody-Associated Autoimmune Encephalitis

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Abstract

Background and Objectives

To assess seizure characteristics in antibody (ab)-associated autoimmune encephalitis (ab + AE) with the 3 most prevalent abs against N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated protein 1 (LGI1), and glutamic acid decarboxylase (GAD).

Methods

Multicenter nationwide prospective cohort study of the German Network for Research in Autoimmune Encephalitis.

Results

Three hundred twenty patients with ab + AE were eligible for analysis: 190 NMDAR+, 89 LGI1+, and 41 GAD+. Seizures were present in 113 (60%) NMDAR+, 69 (78%) LGI1+, and 26 (65%) GAD+ patients and as leading symptoms for diagnosis in 53 (28%) NMDAR+, 47 (53%) LGI+, and 20 (49%) GAD+ patients. Bilateral tonic-clonic seizures occurred with almost equal frequency in NMDAR+ (38/51, 75%) and GAD+ (14/20, 70%) patients, while being less common in LGI1+ patients (27/59, 46%). Focal seizures occurred less frequently in NMDAR+ (67/113; 59%) than in LGI1+ (54/69, 78%) or in GAD+ patients (23/26; 88%). An aura with déjà-vu phenomenon was nearly specific in GAD+ patients (16/20, 80%). Faciobrachial

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Glossary

ab = antibody; **AE** = autoimmune encephalitis; **FBDS** = faciobrachial dystonic seizures; **GAD** = glutamic acid decarboxylase; **GENERATE** = German Network for Research on Autoimmune Encephalitis; **ILAE** = International League Against Epilepsy; **LGI1** = leucine-rich glioma-inactivated protein 1; **mRS** = modified Rankin score; **NMDAR** = N-methyl-D-aspartate receptor; **OR** = odds ratio; **SE** = status epilepticus.

dystonic seizures (FBDS) were uniquely observed in LGI1+ patients (17/59, 29%). Status epilepticus was reported in one-third of NMDAR+ patients, but only rarely in the 2 other groups. The occurrence of seizures was associated with higher disease severity only in NMDAR+ patients.

Discussion

Seizures are a frequent and diagnostically relevant symptom of ab + AE. Whereas NMDAR+ patients had few localizing semiological features, semiology in LGI1+ and GAD+ patients pointed toward a predominant temporal seizure onset. FBDS are pathognomonic for LGI1 + AE. Status epilepticus seems to be more frequent in NMDAR + AE.

Seizures are a prominent symptom in antibody (ab)-associated autoimmune encephalitis (ab + AE).[1,2] Moreover, seizures can occur as the initial symptom prompting further diagnostics.[3-5]

A relevant drawback in diagnosing ab + AE is still the reliance on ab test results, which will only be initiated on suspicion of the treating physician and usually results in a delay of several days or even weeks until diagnosis, thus retarding therapy onset. However, an immediate start of immunotherapy is important for a favorable outcome.[6] A consensus paper has determined a more clinical diagnostic approach for AE.[2] The authors suggest preliminary patient categorization along mainly clinical criteria before ab results are returned allowing early therapy initiation. Both for probable N-methyl-D-aspartate receptor AE (NMDAR + AE) and limbic encephalitis, seizures are mentioned as an important diagnostic feature, but the authors did not make further specification regarding the type of seizures or their semiology.

Nevertheless, more knowledge of seizure semiology in ab + AE could improve the understanding of syndrome characteristics and may facilitate discrimination into the distinct ab + AE subgroups for treating physicians. It is tempting to assume that seizure specifications differ according to cerebral regions affected by distinct ab + AE subgroups. A keystone concerning these aspects was certainly the description of faciobrachial dystonic seizures (FBDS) in AE associated with abs against leucine-rich glioma-inactivated protein 1 (LGI1 + AE).[3] FBDS serve here as a specific prodromal biomarker for LGI1 + AE with tremendous effect on therapy and outcome.[7,8] Apart from FBDS and despite the abovementioned considerations of clinical relevance, descriptions of seizures in ab + AE reports usually remain imprecise even in the diagnostic consensus criteria.[2] Even if semiological features might be not specific for a distinct ab + AE, a better understanding of seizure symptomatology may be important for the diagnostic recognition of AE.

In this study, we aimed to reveal the characteristics of seizures of patients with ab + AE from the database of the German Network for Research on Autoimmune Encephalitis (GENERATE), a nationwide prospective registry for patients with ab + AE. Specifically, we focused on the 3 most common subtypes of AE with antibodies against NMDAR, LGI1, and glutamic acid decarboxylase (GAD). We sought for (1) the proportion of patients with seizures at first presentation and their leading role for making the diagnosis, (2) specificities in seizure semiology according to the detected ab, (3) the prevalence of pathologic EEG findings, and (4) the effect of seizure occurrence on disease severity.

Methods

Patients

We conducted a multicenter nationwide cohort study analyzing registry data of the GENERATE. The study focused on consecutively included patients diagnosed with ab + AE associated with abs against NMDAR, LGI1, or GAD between 2004 and 2016 from 40 collaborating hospitals. In GAD + AE, we applied more strict inclusion criteria concerning the laboratory diagnosis because low-titer GAD abs are currently classified as low specific for an AE.[9]

The laboratory tests for GAD abs in serum had to meet at least 1 of the following criteria: ELISA value >1,000 IU/mL, radioimmunoprecipitation assay >2,000 U/mL, positive labeling cell-based assays (>1:10), or intrathecal ab synthesis (ab index >1.5).

Data were collected at each center by local investigators gathering demographic and clinical information. To assess the severity of the disease, the local investigators provided the modified Rankin score (mRS) at disease maximum in the acute disease stage.

Table 1 Demography, Seizure Frequencies, and Seizures as Leading Symptoms

Demography and seizure frequency	Type of AE			Statistical analysis (*p* value)			
	NMDAR	LGI1	GAD	NMDAR/ GAD/LGI1	NMDAR/LGI1	NMDAR/GAD	LGI1/GAD
No. of patients	190	89	41	—	—	—	—
Male	46 (24%)	49 (55%)	5 (12%)	**<0.001**[a]	**<0.001**[b] **(OR 0.3)**	0.101[b]	**<0.001**[b] **(OR 8.8)**
Tumor	33 (17%)	3 (3%)	0	**<0.001**[a]	**<0.001**[b] **(OR 6.0)**	**<0.001**[b] **(OR 1.2)**	0.551[b]
Median age at onset, y (IQR)	34 (20.9–45.1)	63 (53.5–71.0)	50 (34.1–61.1)	**<0.001**[c]	**<0.001**[c]	**<0.001**[c]	**0.007**[c]
Seizures	113 (59.5%)	69 (77.5%)	26 (65.0%)	**0.01**[a]	**0.003**[b] **(OR 0.4)**	0.64[b]	0.09[b]
Semiology							
Bilateral tonic-clonic only	39/113 (35%)	15/69 (22%)	3/26 (12%)	**0.026**[a]	0.094[b]	**0.031**[b] **(OR 4.0)**	0.381[b]
Focal only	27/113 (24%)	33/69 (48%)	8/26 (31%)	**0.004**[a]	**<0.001**[b] **(OR 0.3)**	0.462[b]	0.167[b]
Both	40/113 (35%)	21/69 (30%)	15/26 (58%)	**0,045**[a]	0.521[b]	**0.046**[b] **(OR 0.4)**	**0.019**[b] **(OR 0.3)**
Seizure as a leading symptom	53/190 (28%)	47/89 (53%)	20/41 (49%)	**<0.001**[a]	**<0.001**[b] **(OR 0.3)**	**0.015**[b] **(OR 0.4)**	0.709[b]

Abbreviations: AE = autoimmune encephalitis; GAD = glutamic acid decarboxylase; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = N-methyl-D-aspartate receptor.
[a] The Freeman-Halton test.
[b] The Fisher Exact test.
[c] The Kruskal-Wallis test and Bonferroni correction.

The seizure semiology was categorized according to the current classification of the International League Against Epilepsy (ILAE).[10] In the patient population with focal seizures, patient charts were analyzed to retrieve more detailed information about focal seizure semiology. Furthermore, we assessed EEG findings from the database. This study primarily focused on the early stage of AE (i.e., the first presentation at the corresponding center where the diagnosis of ab + AE was performed).

Standard Protocol Approvals, Registrations, and Patient Consents

Initial institutional review board approval was given by the ethical advisory board of the University of Luebeck, Germany, (reference number: 13–162) and consecutively by the regional ethical advisory boards of all participating centers. Written informed consent was obtained from every patient or their representative.

Statistical Analysis

The SPSS statistic computer package (version 25.0; IBM Corporation) was used for all statistical analyses. Categorical variables were presented as numbers (n/N) and percentages. Values were given as median and interquartile range.

Group comparisons of categorical variables (e.g., sex of the patients) were hierarchically performed first with the Freeman-Halton test and subsequently between 2 groups with the Fisher exact test. The Kruskal-Wallis test and Bonferroni correction for multiple tests were used to compare metrical data between 3 or 2 groups, respectively. All tests were 2-tailed; p values < 0.05 were considered statistically significant.

Data Availability

Anonymized data not published within this article will be made available on reasonable request from qualified investigators.

Results

Patient Characteristics

We screened 387 patients with ab + AE (205 NMDAR+, 101 LGI1+, and 81 GAD+) from the GENERATE database enrolled until 2016. Sixty-seven patients had to be excluded because of incomplete data in the documentary files. Finally, 320 patients were analyzed for this study: 190 (59%) had abs against NMDAR, 89 (28%) against LGI1, and 41 (13%) against GAD (Table 1). Corroborating previous studies, LGI1+ patients were more often males (55%) than NMDAR+ (24%) and GAD+ (12%) patients (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p < 0.001$, LGI1+/GAD+ $p < 0.001$). NMDAR+ patients were significantly younger (median: 34 years) at onset than LGI1+ (median: 63 years) and GAD+ patients (median: 50 years; NMDAR+/LGI1+/GAD+, NMDAR+/LGI1+, and NMDAR+/GAD+ $p < 0.001$ respectively). Furthermore, a paraneoplastic condition was moderately frequent in NMDAR+ patients (17%),

Table 2 Demographic Data for Patients With ab + AE With and Without Seizures

	Sz+ (N)	Sz− (N)	Statistical analysis (*p* value)
NMDAR (N = 190)	113 (60%)	77 (41%)	—
Male	25 (22%)	21 (27%)	0.49[a]
Tumor	19 (17%)	14 (18%)	0.85[a]
Median age at onset, y (IQR)	26 (19.0–38.2)	35 (23.2–49.4)	**0.003**[b]
LGI1 (N = 89)	69 (78%)	20 (23%)	—
Male	36 (52%)	13 (65%)	0.44[a]
Tumor	2 (3%)	1 (5%)	0.54[a]
Median age at onset, y (IQR)	64 (53.5–70.6)	69 (53.0–74.5)	0.28[b]
GAD (N = 41)	26 (63%)	15 (37%)	—
Male	3 (12%)	2 (13%)	1.0[a]
Tumor	0	0	—
Median age at onset, y (IQR)	37 (31.3–52.9)	62 (59.1–71.9)	**<0.001**[b]

Abbreviations: ab = antibody; AE = autoimmune encephalitis; GAD = glutamic acid decarboxylase; IQR = interquartile range; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = N-methyl-D-aspartate receptor; Sz− = without seizures; Sz+ = with seizures.
[a] The Fisher exact test.
[b] The Kruskal-Wallis test and Bonferroni correction.

rare in LGI1+ (3%), and absent in GAD+ patients (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p < 0.001$, and NMDAR+/GAD+ $p < 0.001$).

Proportion of Patients With Seizures

Of importance, seizures were present in almost 2-thirds of patients with ab + AE (N = 208/320; 65%) at the early stage of disease. In detail, 113/190 (60%) patients with NMDAR + AE, 69/89 (78%) patients with LGI1 + AE, and 26/41 (65%) patients with GAD + AE experienced seizures. Seizures occurred less frequently in NMDAR+ than in LGI1+ patients (NMDAR+/LGI1+/GAD+ $p = 0.01$, NMDAR+/LGI1+ $p = 0.003$, Table 1). Seizures as a leading symptom to prompt further diagnostics were seen 2.9 times more often in LGI1+ and 2.4 times more often in GAD+ than in NMDAR+ patients (NMDAR+/LGI1+/GAD+ $p = 0.01$, NMDAR+/LGI1+ $p < 0.001$, and NMDAR+/GAD+ $p = 0.02$, Table 1).

When comparing characteristics in the individual ab + AE subgroups for patients with and without seizures, we found that NMDAR+ and GAD+ patients with seizures were younger than those without (NMDAR+ $p = 0.003$; GAD+ $p < 0.001$), whereas other demographical characteristics did not differ whether seizures were present or not (for details, see Table 2).

Semiology of Seizures

A detailed description of seizure semiology was available in 51 NMDAR+, 59 LGI1+, and 20 GAD+ patients, which is summarized in Table 3. Knowledge of the specific focal seizure onset was required to apply the ILAE classification guidelines.[10]

Focal Seizures

Whereas focal seizures without impaired awareness were observed similarly often throughout all 3 ab + AE subgroups, focal seizures with impaired awareness were more frequently found in GAD+ patients (17/20, 85%) and in NMDAR+ patients (35/51, 69%) than in LGI1+ patients (28/59, 48%; NMDAR+/LGI1+/GAD+ $p = 0.004$, NMDAR+/LGI1+ $p = 0.03$, and LGI1+/GAD+ $p = 0.004$). FBDS were found solely in 17/59 (29%) of LGI1+ patients (NMDAR/LGI1/GAD $p < 0.001$).

Motor-onset seizures were most frequently observed in NMDAR+ patients (31/51, 61%) with a broad spectrum of symptoms. Vice versa, in LGI1+ patients, motor-onset seizures were the least often observed among all 3 ab + AE subgroups with 19% of cases (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p < 0.001$, and LGI1+/GAD+ $p = 0.009$). Of note, FBDS were considered a unique semiology and were separately analyzed. In GAD+ patients, the phenotype of motor-onset seizures was less variable. In this study, automatisms were the key feature being present in all GAD+ patients with motor-onset seizures (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/GAD+ $p = 0.02$, and LGI1+/GAD+ $p < 0.001$): the likelihood of automatism was 4.1 times higher than in NMDAR+ and 10.8 times higher than in LGI1+ patients, whereas other motor signs were scarcely or never reported in GAD+ patients. A clonic motor onset was only seen in NMDAR+ patients (5/51; 10%) (NMDAR+/LGI1+/GAD+ $p = 0.02$, NMDAR+/LGI1+ $p = 0.02$, and NMDAR+/GAD+ $p = 0.31$). Moreover, a myoclonic motor onset was found in NMDAR+ patients in 10/51 (20%) cases,

Table 3 Focal Seizures and Their Semiology

	Type of AE			Statistical analysis (*p* value)			
Focal seizure semiology	**NMDAR (n = 51)**	**LGI1 (n = 59)**	**GAD 65 (n = 20)**	**NMDAR/LGI1/GAD[a]**	**NMDAR/LGI1[b]**	**NMDAR/GAD[b]**	**LGI1/GAD[b]**
Without impaired awareness	21/51 (41.%)	34/59 (58%)	13/20 (65%)	0.113	—	—	—
With impaired awareness	35/51 (69%)	28/59 (48%)	17/20 (85%)	**0.004**	**0.034 (OR 2.4)**	0.236	**0.004 (OR 0.2)**
Motor onset	31/51 (61%)	11/59 (19%)	10/20 (50%)	**<0.001**	**<0.001 (OR 6.8)**	0.435	**0.009 (OR 0.2)**
Automatism	10/31 (32%)	5/11 (46%)	10/10 (100%)	**<0.001**	0.103	**0.018 (OR 0.2)**	**<0.001 (OR 0.1)**
Clonic	5/31 (10%)	0/11 (0%)	0/10 (0%)	**0.022**	**0.019 (OR n.d.)**	0.312	—
Hyperkinetic	0/31 (0%)	0/11 (0%)	1/10 (10%)	0.154		0.282	0.253
Myoclonic	10/31 (32%)	3/11 (27%)	0/10 (0%)	**0.015**	**0.035 (OR 4.6)**	0.053	0.567
Tonic	6/31 (19%)	3/11 (27%)	1/10 (10%)	0.501	0.298	0.664	1
Nonmotor onset	15/51 (29%)	29/59 (49%)	16/20 (80%)	**<0.001**	0.051	**<0.001 (OR 0.1)**	**0.019 (OR 4.1)**
Autonomic	1/15 (7%)	16/29 (55%)	8/16 (50%)	**<0.001**	**<0.001 (OR 0.1)**	**<0.001 (OR 0.03)**	0.399
Behavioral arrest	0/15 (0%)	5/29 (17%)	2/16 (13%)	**0.048**	0.06	0.076	1
Cognitive	9/15 (60%)	5/29 (17%)	7/16 (35%)	**0.022**	0.165	0.128	**0.009 (OR 0.2)**
Emotional	1/15 (7%)	3/29 (10%)	2/16 (13%)	0.312	0.622	0.189	0.596
Sensory	6/15 (40%)	10/29 (35%)	6/16 (38%)	0.188	0.589	0.084	0.216
FBDS	0/51 (0%)	17/59 (29%)	0/20 (0%)	**<0.001**	**<0.001 (OR n.d.)**	—	**0.004 (OR n.d.)**

Abbreviations: AE = autoimmune encephalitis; FBDS = faciobrachial dystonic seizures; GAD = glutamic acid decarboxylase; IQR = interquartile range; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = N-methyl-D-aspartate-receptor; OR = odds ratio.
[a] The Freeman-Halton test.
[b] The Fisher exact test.

whereas it was rare in LGI1+ (3/59, 5%) and absent in GAD+ patients (NMDAR+/LGI1+/GAD+ $p = 0.02$, NMDAR+/LGI1+ $p = 0.04$, and NMDAR+/GAD+ $p = 0.05$).

Nonmotor-onset seizures occurred more frequently in GAD+-patients (16/20, 80%) than in one of the other ab + AE subgroups (NMDAR+/LGI1+/GAD+ $p \leq 0.001$, NMDAR+/GAD+ $p < 0.001$, and LGI1+/GAD+ $p = 0.02$). Whereas ictal autonomic symptoms were found in approximately half of the GAD+ (8/16; 50%) and LGI1+ (16/29, 55%) patients with nonmotor-onset seizures, they were very rare in NMDAR+ (1/51, 2%) patients (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p < 0.001$, and NMDAR+/GAD+ $p < 0.001$). Notably, pilomotor seizures as a particular subtype of autonomic seizures were reported only in LGI1+ (9/59, 15%) and GAD+ (1/20, 5%) patients. Ictal cognitive symptoms were seldom in LGI1+ patients (5/59, 9%) compared with GAD+ patients (7/20, 35%, $p = 0.009$).

Phenomenology of Aura

In addition, we investigated auras as a key element of seizures that may provide information regarding the seizure onset zone. The detailed analysis of aura is summarized in Table 4. Auras were most prevalent in GAD+ patients (16/20, 80%; NMDAR+/LGI1+/GAD+ $p < 0.001$), seen 21.5 times more often than in NMDAR+ (8/51, 16%, $p < 0.001$) and 5.4 times more often than in LGI1+ patients (25/59, 42%, $p = 0.004$). Déjà vu seemed to serve as a specific aura phenomenon of GAD+ patients (7/20, 35%) compared with that of NMDAR+ (2/51, 2%) and LGI1+ patients (0/59, 0%; NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/GAD+ $p < 0.001$, and LGI1+/GAD+ $p < 0.001$). An epigastric aura was equally common in LGI1+ (12/59, 20%) and GAD+ (6/20, 30%) patients, but rare in NMDAR+ (1/51, 2%) patients (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p = 0.003$, NMDAR+/GAD+ $p = 0.002$).

Bilateral Tonic-Clonic Seizures

Bilateral tonic-clonic seizures were detected in all ab + AE subgroups (79/130, 61%); they occurred with almost equal frequency in NMDAR+ (38/51, 75%) and in GAD+ (14/20, 70%) patients, while being less common in LGI1+ patients (27/59, 46%) (NMDAR+/LGI1+/GAD+ $p = 0.006$, NMDAR+/LGI1+ $p = 0.003$, NMDAR+/GAD+ $p = 0.77$, and LGI1+/GAD+ $p = 0.074$, Table 5).

Table 4 Phenomenology of Aura

Aura semiology	Type of AE			Statistical analysis (*p* value)			
	NMDAR 8 (n = 51)	LGI1 (n = 59)	GAD 65 (n = 20)	NMDAR/LGI1/GAD[a]	NMDAR/LGI1[b]	NMDAR/GAD[b]	LGI1/GAD[b]
Aura reported	8 (16%)	25 (42%)	16 (80%)	**<0.001**	**0.003 (OR 0.3)**	**<0.001 (OR 0.1)**	**0.004 (OR 0.2)**
Fear	1 (2%)	3 (5%)	1 (5%)	0.578	0.622	0.487	1
Deja-vu	2 (4%)	0 (0%)	7 (35%)	**<0.001**	0.213	**<0.001 (OR 0.1)**	**<0.001 (n.d.)**
Psychic	1 (2%)	3 (5%)	2 (10%)	0.312	0.622	0.189	0.596
Epigastric	1 (2%)	12 (20%)	6 (30%)	**<0.001**	**0.003 (OR 0.1)**	**0.002 (OR 0.1)**	0.373
Vegetative (other than epigastric)	0 (0%)	1 (2%)	1 (5%)	0.285	1	0.282	0.445
Sensory	4 (8%)	4 (7%)	3 (15%)	0.523	1	0.394	0.361
Auditory	0 (0%)	0 (0%)	1 (5%)	0.154	—	0.282	0.253
Visual	0 (0%)	0 (0%)	1 (5%)	0.154	—	0.282	0.253
Olfactory	0 (0%)	2 (3%)	1 (5%)	0.378	0.498	0.282	1
Dizziness	0 (0%)	3 (5%)	2 (10%)	0.104	0.247	0.076	0.596
Unspecific	0 (0%)	1 (17%)	2 (10%)	0.062	1	0.076	0.156

Abbreviations: AE = autoimmune encephalitis; GAD = glutamic acid decarboxylase; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = N-methyl-d-aspartate-receptor; OR = odds ratio.
[a] The Freeman-Halton test.
[b] The Fisher exact test.

Status Epilepticus

Because the information, whether status epilepticus (SE) occurred, was a mandatory entry in the database, we could analyze all patients with seizures regarding this issue. SE was reported in more than a quarter of NMDAR+ patients with seizures (30/113, 26.5%), whereas it was rare in the other 2 ab + AE subgroups with only 4/69 (6%) LGI1+ and 1/26 (4%) GAD+ patients affected (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p < 0.001$, NMDAR+/GAD+ $p = 0.009$). Thus, NMDAR + patients had a 5.8 and 9.0 times higher probability to experience SE in comparison with LGI1+ and GAD+, respectively (Table 5).

EEG

EEG data were available in most cases (NMDAR+ 164/190, 86%; LGI1+ 81/89, 91%, GAD+ 32/41, 78%) with pathologic abnormalities in most of the ab + AE patients (NMDAR+ 73%, LGI1+ 68% and GAD+ 75%, $p = 0.62$). Despite the fact that generalized slowing was found mainly in NMDAR + patients, all other parameters did not differ in the ab + AE subgroups: generalized slowing in NMDAR + AE patients (48%) has been reported twice as often than in LGI1+ (21%) and 3 times more often than in GAD+ (16%) patients (NMDAR+/LGI1+/GAD+ $p < 0.001$, NMDAR+/LGI1+ $p < 0.001$, NMDAR+/GAD+ $p < 0.001$, eTable 1, links.lww.com/NXI/A747).

We additionally analyzed whether the EEG differed between patients with and without seizures within the ab + AE subgroups (eTable 2, links.lww.com/NXI/A747). In general, EEG was more often pathologic in patients with seizures in the NMDAR+ ($p = 0.002$) and GAD+ ($p = 0.005$) subgroups than in the LGI1+ subgroup with seizures in comparison with the subgroup without seizures, respectively. The analysis of epileptiform discharges and ictal patterns was of particular interest. Whereas in NMDAR + patients, both epileptiform discharges and ictal patterns were not significantly different in patients with and without clinical seizures, epileptiform discharges were observed only in GAD+ patients with clinical seizures ($p = 0.029$). In LGI1+ and GAD+ patients, ictal patterns were detected only in patients with clinical seizures (LGI1+ 15/63, $p = 0.02$, GAD+ 6/25, $p = 0.3$).

Seizures and mRS at Disease Maximum

In general, the mRS was significantly higher in NMDAR+ patients in comparison with LGI1+ and GAD+ patients (Figure 1). In total, 60% of NMDAR+ patients revealed a mRS >4, whereas only 21% GAD+ and 20% LGI1+ patients did (NMDAR+/LGI1+/GAD+ $p < 0.001$, LGI1+/GAD+ $p < 0.001$, NMDAR+/GAD+ $p < 0.001$).

Of note, within the NMDAR+ subgroup, the occurrence of seizures was associated with a 2.8-fold increased risk to show a higher level of disease severity (mRS >4, odds ratio [OR] = 2.800; $p < 0.001$, Figure 1B). SE in NMDAR+ patients even leads to 5.0-fold increased probability to express an mRS >4 than in NMDAR+ patients without seizures (OR = 5.063; $p = 0.001$). By contrast, in LGI1+ and GAD+

Table 5 Bilateral Tonic-Clonic Seizures and Status Epilepticus

	Type of AE			Statistical analysis (*p* value)			
Seizure semiology	**NMDAR**	**LGI1**	**GAD 65**	**NMDAR/LGI1/GAD[a]**	**NMDAR/LGI1[b]**	**NMDAR/GAD[b]**	**LGI1/GAD[b]**
Tonic clonic seizures	38/51 (75%)	27/59 (46%)	14/20 (70%)	**0.006**	**0.003 (OR 3.5)**	0.769	0.074
Status epilepticus	30/113 (27%)	4/69 (6%)	1/26 (4%)	**<0.001**	**<0.001 (OR 5.8)**	**0.009 (OR 9.0)**	1.000
Focal status epilepticus	16/30 (53%)	1/4 (25%)	0/1 (0%)	—	—	—	—
Tonic-clonic status epilepticus	11/30 (37%)	2/4 (50%)	1/1 (100%)	—	—	—	—
Unclassified	3/30 (10%)	1/4 (25%)	0/1 (0%)	—	—	—	—

Abbreviations: AE = autoimmune encephalitis; GAD = glutamic acid decarboxylase; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = N-methyl-d-aspartate-receptor; OR = odds ratio.
[a] The Freeman-Halton test.
[b] The Fisher exact test.

patients, the occurrence of seizures had no significant effect on the level of disability at disease maximum (Figure 1B).

Discussion

Seizures are a common and often leading symptom in early stages of ab + AE. In this study, we provide a large dataset of well-characterized ab + AE patients with documented seizures. In our nationwide multicentric cohort, 2-thirds of all patients with AE positive for the 3 most prevalent abs against NMDAR, LGI1, or GAD presented with seizures at the early stages of disease.

In approximately half of the LGI1+ and GAD+ patients, seizures were the dominating symptom, leading to further diagnostics. NMDAR+ patients were less likely to experience seizures at the early stages compared with the other 2 ab + AE subgroups, and these were indicative for diagnosis only in approximately one-third of cases. If seizures occurred in NMDAR+, they had a significant effect on disease severity, particularly if they evolved into SE.

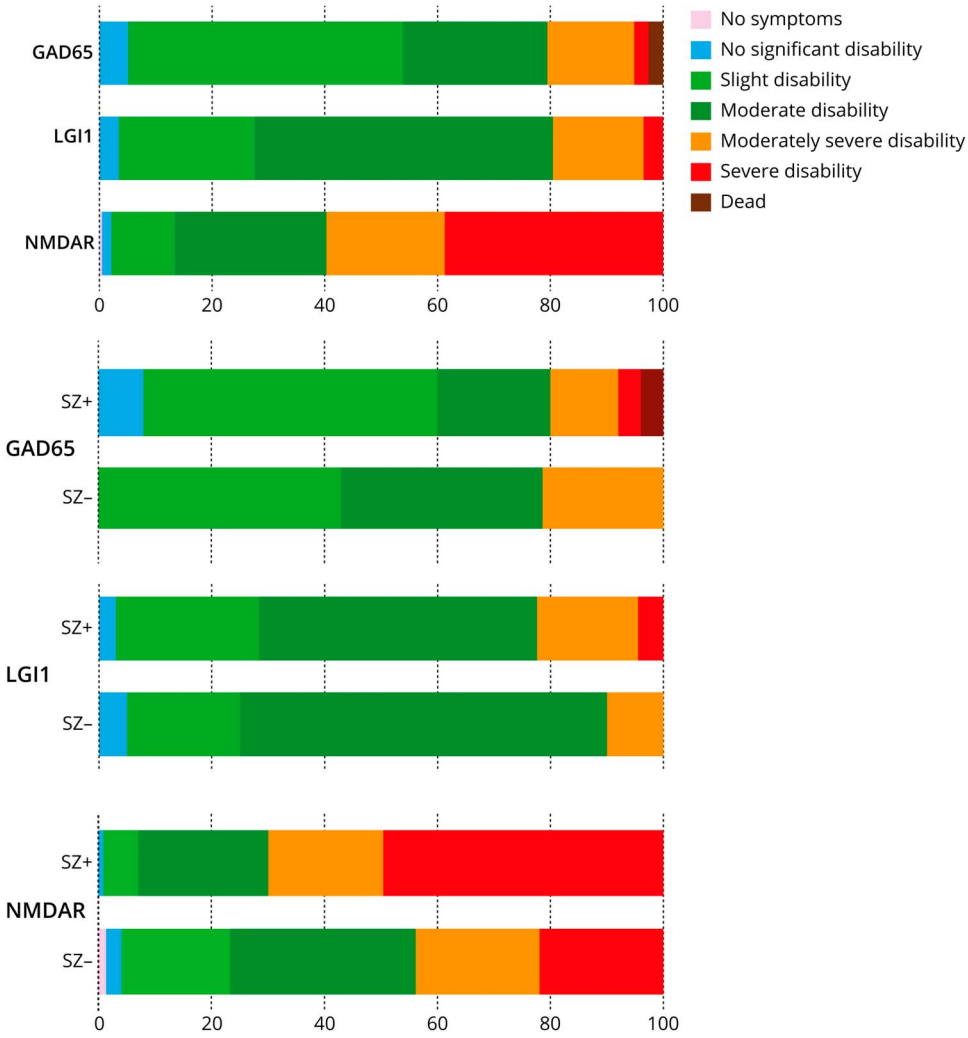
The occurrence of seizures and their semiology differed throughout the ab + AE subgroups, revealing several characteristic features. Except for the LGI1+ subgroup, patients with seizures were younger than patients without seizures.

According to the more widespread and diffuse cerebral lesion pattern in NMDAR + AE, patients presented with focal and frequent bilateral tonic-clonic seizures. Semiological features of focal seizures in the NMDAR+ subgroup were diverse regarding impaired awareness and motor or nonmotor onset. In motor-onset seizures, clonic and myoclonic features were characteristics for NMDAR+ patients. An aura was uncommon in this ab + AE subgroup compared with that in both LGI1+ and GAD+ patients. On the contrary, bilateral tonic-clonic seizures were typical in NMDAR+ patients, and SE was present in 27% of NMDAR+ cases with seizures, whereas it was a rarity in the 2 other ab + AE subgroups.

In summary, our study points to diverse sites of seizure origins in NMDAR + including the frontal motor zones, which is in line with the findings of Niehusmann et al.[11] Thus, our results do not support the common hypothesis that most seizures originate from the temporal lobe in NMDAR+.[12] Extrapyramidal movements are very common in NMDAR+ patients, particularly orofacial dyskinesia, which might be mistaken for temporal seizure symptoms.[13] In general, the differentiation between epileptic seizures and extrapyramidal movements within the NMDAR+ population is challenging. Studies with continuous video-EEG monitoring are required to further investigate and clarify these aspects. Similarly, a more frequent application of video-EEG monitoring would also help to determine more precisely the incidence of SE in NMDAR + AE. In our study, the proportion of SE was highest in NMDAR+ patients with 27%. These data should be interpreted with caution because we were not able to explicitly reanalyze the EEG data from each center. A previous study revealed that in NMDAR+ AE, abnormal EEG findings such as rhythmic delta activity, movement disorders, and impaired awareness are frequently misinterpreted as SE.[14] In a recent systemic review dealing with EEG abnormalities and seizures in AE, "SE on EEG" was even found in only 0.2% of NMDAR+ patients.[15] Considering the diagnostic difficulties mentioned earlier, this result should be also viewed with caution because the classification, whether SE was present or not, thus considerably depended largely on the epileptological expertise of the reporting physician.

In our LGI1+ population, a significant proportion of patients experienced only focal seizures (48%). Thereby, focal seizures with and without impaired awareness occurred with a similar prevalence. The more detailed analysis revealed that nonmotor-seizure onset with autonomic features was the most typical semiology in LGI1+ patients. An aura was reported in 42% of cases, in half of them as an epigastric aura, suggesting a temporal origin. As a peculiar symptom, we observed pilomotor seizures in 15% of the LGI1+ patients, which also indicates involvement of the limbic structures. In

Figure 1 Scores of the Modified Rankin Scale (mRS) at Disease Maximum in the Acute Stage



(A) Shows the distribution of scores of all patients in the 3 subgroups of ab + AE. mRS was significantly higher in NMDAR+ patients in comparison with that in LGI1+ (mRS >4, OR = 11.2, $p < 0.001$) and GAD+ patients (mRS >4, OR = 6.2, $p < 0.001$). (B) Shows the scores in patients with and without seizures within the individual ab + subgroups. In the NMDAR+ subgroup, the occurrence of seizures was associated with a 2.8-fold increased risk to show a higher level of disease severity (mRS >4, OR = 2.800; $p < 0.001$), whereas it had no significant effect in LGI1+ and GAD+ patients. GAD = glutamic acid decarboxylase; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = N-methyl-D-aspartate receptor.

line with these findings, previous smaller case series also reported seizures with temporal semiology with autonomic symptoms and impaired awareness as main seizure type in LGI1 + AE.[16,17] Besides the temporal lobe seizures, FBDS were frequently observed in our LGI1+ cohort (28%), and their occurrence was unique in the LGI1+ subgroup. Hence, our study adds further evidence to the assumption that FBDS can be nearly considered as pathognomonic for LGI1 + AE and are not detected in other forms of AE.[3,12] The frequency of FBDS in our LGI1+ cohort might be underestimated due to challenges of detecting and categorizing this seizure type properly in the beginning phase of the GENERATE database. We included patients from 2006 to 2016, and the awareness of FBDS has just started since their first description in 2011.[3] Hence, FBDS might be missed in early LGI1 patients before 2011. In previous case studies and smaller patient series, the frequency of FBDS in LGI1 were 32%,[18] 48%,[17] and 69%.[16]

GAD+ patients presented with both focal and bilateral tonic-clonic seizures. Focal seizures occurred predominantly with impaired awareness, with motor onset or nonmotor onset. Typical features were automatisms in motor-onset seizures. Regarding aura phenomenon, déjà vu was nearly specific for GAD+ patients. The epigastric aura was the second most common aura phenomenon. Altogether, seizure semiology in GAD+ patients is characteristic for a temporal seizure origin. SE was very rare in this ab + subgroup. A comprehensive analysis of seizure semiology in GAD+ patients is lacking so far. In previous studies of GAD + AE, descriptions of seizure semiology mainly simplified to terms such as "localization-related seizures, temporal lobe seizures, or seizures with temporal semiology."[19-21] Hence, our study provides unique information on detailed semiological features of a large cohort of GAD+ patients. Consistent with the literature, the limbic structures appear thereby the predominant target in GAD + AE with seizures.[9,20] Of note, few recent case reports discuss musicogenic reflex seizures as typical semiology in GAD + AE, which were not detected in our analysis.[22-24] A possible explanation could be underreporting because this association was recognized after the inclusion period of this study.

Nevertheless, the occurrence of musicogenic reflex seizures in GAD+ patients is in line with a predominant temporal seizure onset in this ab + AE subgroup. Besides the clinical constellation of intractable temporal lobe seizures, a second scenario with acute onset and SE has been described in GAD + AE.[19,25,26] In this study, we detected only 1 patient with SE; thus, SE may rather be a rare clinical manifestation in GAD + AE.

Despite the wide use of EEG in ab + AE in clinical practice, there exist only few systematic data on that subject regarding sensitivity and specificity of pathologic findings, especially in assessing the risk of seizures. The best knowledge exists for pathologic EEG findings in NMDAR + AE with diffuse and focal slowing as most relevant findings.[13,27] In a recent study focusing on the predictive value of EEG recordings in NMDAR+ adult and children patients, 96% of adults and all children had abnormal findings at their first EEG recording, pointing to a high sensitivity. Furthermore, an abnormal posterior EEG rhythm at onset was considered to have a negative predictive value for clinical outcome.[27] In studies with LGI1+ patients, approximately 25% of patients showed focal slowing,[17] and approximately 30% of patients had epileptiform discharges.[17,28] We are not aware of a larger cohort of GAD+ patients exploring systemic EEG data. There are only a few cases in heterogenic ab + AE patient cohorts reporting EEG findings, revealing mainly focal interictal discharges.[29,30]

In our cohort, we could confirm previous findings that focal and generalized slowing are the most prevalent EEG findings. Generalized slowing was present in nearly half of the NMDAR+ patients but only in 21% of LGI1+ and 16% of GAD+ patients, once again reflecting the more diffuse distribution in NMDAR + AE. Of interest, NMDAR+ patients had both epileptiform discharges and ictal patterns irrespective of clinical seizure occurrence, whereas ictal patterns in LGI1+ and GAD+ patients were only detected in patients with clinical seizures. However, we found no significant relevance of EEG to predict the risk of having seizures in the early stage of disease.

Our study has several limitations. First, we included only patients from the GENERATE database, which is a free alliance of hospitals with different medical care standards throughout Germany. Thus, the study may bear a relevant risk for a selection bias. Indeed, such a selection bias can be assumed in many if not almost all other reports on the topic of ab + AE. To our knowledge, only the group of Titulaer from Rotterdam, the Netherlands, reported country-wide epidemiologic data of ab + AE because they serve as the only national reference ab laboratory in Netherlands.[18] All other reports share the problem of data retrieved from specialized reference laboratory databases or from single specialized centers. With the GENERATE cohort, we aim to overcome the limitations of small monocentric studies or studies of some specialized centers. The nationwide approach widens the spectrum of patients reported not only from specialized tertiary but also from other medical care standard centers involved in the treatment of AE patients (generate-net.de). A further argument against relevant selection bias in our population is the matching demographical distribution with previous reports of the distinct ab + AE subgroups. NMDAR+ patients are mainly females of middle or younger age with a tumor rate of approximately 20%.[13,18] LGI1+ patients are predominantly older males with rare tumor association,[3,17] and finally, GAD+ patients are mainly middle-aged women without tumor association.[9,19,31] Second, the data quality in a multicentric registry study has to be critically questioned. Indeed, there could be a relevant information gap because we were not able to reevaluate in person all data included in the database. Instead, we asked the collaborating centers to provide anonymized full and detailed descriptions of seizure semiologies and EEG recordings. We therefore cannot exclude some missing details according to the level of epileptological expertise in the different sites. Third, our aim was to assess seizure characteristics in the early stage of ab-associated AE. The distinction between acute symptomatic seizures due to an active encephalitis and autoimmune-associated epilepsy as a chronic disease, as conceptualized by Geis et al.,[1] was behind the scope of our study and will be addressed in future investigations. After a subset of patients with coexisting NMDAR and myelin oligodendrocyte glycoprotein abs was first reported in 2014,[32] this topic has gained increasing interest. However, the clinical relevance of these coexisting antibodies remains controversial at present.[33] Because these findings were largely unknown during patient recruitment in this study, we cannot report any further results regarding this.

Seizures are a frequent and important clinical symptom in the early stages of ab + AE with abs against NMDAR, LGI1, and GAD with relevant effect on diagnosis and disease severity. Patients with NMDAR + AE had only few characteristic semiological features according to the more diffuse cerebral affection, but developing seizures is associated with a more severe disease course. By contrast, semiology in LGI1+ and GAD+ patients clearly pointed to a more focal and temporal seizure onset. FBDS are pathognomonic for LGI1+AE. SE seems to be more frequent for NMDAR + AE.

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