

Antiepileptic drug therapy in patients with autoimmune epilepsy

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ABSTRACT

Objective: We aimed to report the pattern of usage and efficacy of antiepileptic drugs (AEDs) in patients with autoimmune epilepsy (AE).

Methods: We retrospectively studied the Mayo Clinic's electronic medical record of patients with AE in which seizures were the main presenting feature. Clinical data, including demographics, seizure characteristics, type of AED and immunotherapy used, presence of neural antibody, and treatment outcomes, were reviewed.

Results: The medical records of 252 adult patients diagnosed with autoimmune encephalitis and paraneoplastic disorders were reviewed. Seizure was the initial presentation in 50 patients (20%). Serum and/or CSF autoantibodies were detected in 41 (82%) patients, and 38 (76%) patients had neural autoantibodies. The majority ($n = 43$, 86%) received at least 1 form of immunotherapy in combination with AEDs, while the remainder received AEDs alone. Twenty-seven patients (54%) became seizure free: 18 (36%) with immunotherapy, 5 (10%) with AEDs alone, and 4 (8%) with AEDs after immunotherapy failure. Levetiracetam was the most commonly used (42/50); however, it was associated with 0% seizure-free response. AED seizure-free responses occurred with carbamazepine ($n = 3$) [3/16, 18.8%], lacosamide ($n = 3$) [3/18, 16.6%] with phenytoin ($n = 1$) [1/8, 12.5%], or oxcarbazepine ($n = 2$) [2/11, 18.1%]. Regardless of the type of therapy, voltage-gated potassium channel-complex antibody-positive patients were more likely to become seizure free compared with glutamic acid decarboxylase 65 antibody-positive cases (12/17 vs 2/10, $p = 0.0183$).

Conclusions: In select patients, AEDs alone were effective in controlling seizures. AEDs with sodium channel blocking properties resulted in seizure freedom in a few cases. Prospective studies are needed to clarify AED selection and to elucidate their immunomodulatory properties in AE.

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GLOSSARY

AE = autoimmune epilepsy; **AED** = antiepileptic drug; **EMR** = electronic medical record; **G-AChR** = ganglionic acetylcholine receptor; **NMDAR** = NMDA receptor; **TNF α** = tumor necrosis factor- α ; **TPO** = thyroid peroxidase; **VGKC-complex** = voltage-gated potassium channel-complex.

Autoimmune epilepsy (AE) has been linked to both antineural antibodies targeting neural intracellular proteins (GAD65, ANNA-1, Ma, etc) and cell surface antigens (voltage-gated potassium channel-complex [VGKC-complex], NMDA receptor, AMPA, GABA-B, mGluR5, etc). AE can occasionally occur in the absence of detected neural antibodies as well.¹ Valuable clinical clues for AE are subacute onset, an unusually high seizure frequency, intraindividual seizure variability or multifocality, antiepileptic drug (AEDs) resistance, personal or family history of autoimmunity, or history of recent or past neoplasia.² Seizures occur as an early and prominent feature in AE, and these are characteristically refractory to conventional AED therapy.¹

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Although intractability is a common feature in AE, some respond to AEDs, and they remain an important aspect of therapy. The role of AEDs in these patients is also relevant as even after controlling the inflammatory response, some patients remain at risk of recurrent seizures, particularly if cerebral damage occurred during the acute encephalitic phase of the illness. Some AEDs affect cellular and humoral immune responses.^{3–6} For example, carbamazepine and valproate have been shown to increase the serum levels of IL-1 β , IL-2, IL-4, IL-6, IL-17, and tumor necrosis factor- α (TNF α) production.^{4,5} At this time, no single AED stands out as superior to others in AE, and the medically refractory nature of seizures in these patients is typically emphasized. However, occasional patients do respond to AED treatment, and it is not currently known if this occurs with medications featuring particular mechanisms of action. In this study, we aimed to explore the pattern of

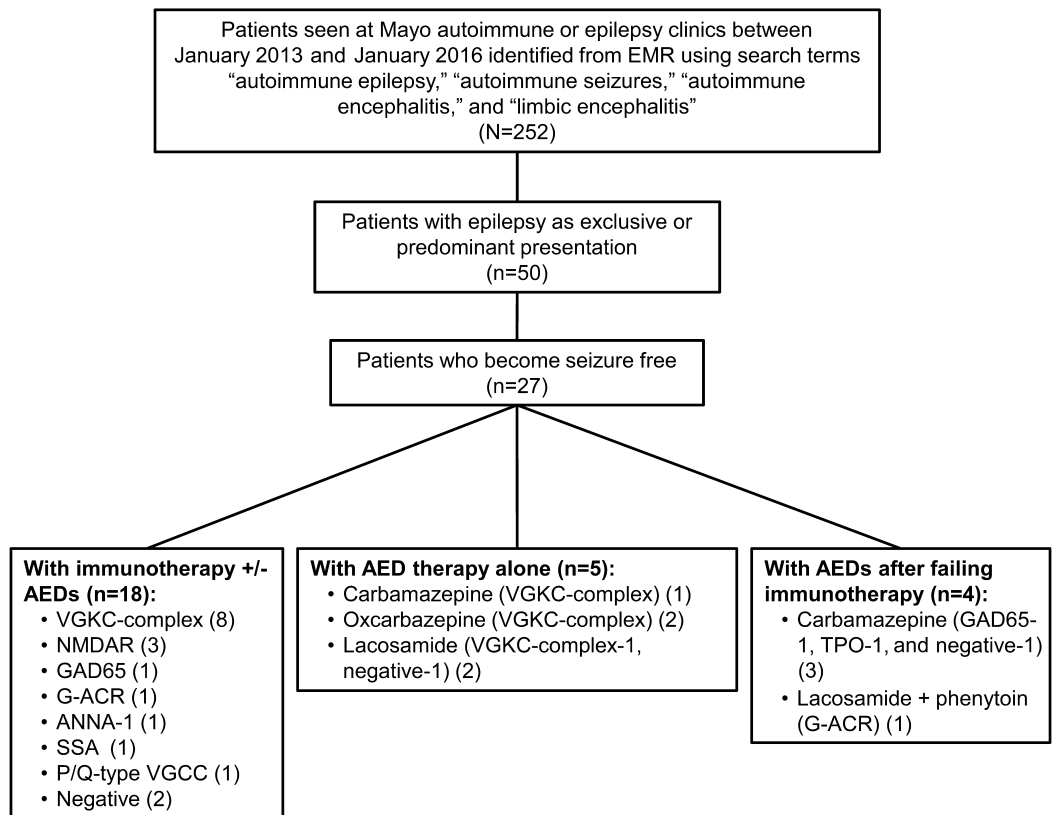
usage and relative efficacy of AEDs in patients with AE.

METHODS To identify all relevant adult cases of AE, we searched the medical record index system of the Mayo Clinic, Rochester, for the terms “autoimmune encephalitis,” “autoimmune epilepsy,” “autoimmune seizure,” and “limbic encephalitis” from January 1, 2013, through December 31, 2015. Our search resulted in 252 cases. Among these, 50 patients were identified who fulfilled the following criteria: (1) seizures as the exclusive or predominant presenting complaint and (2) an autoimmune etiology suspected on the basis of clinical presentation, inflammatory CSF, MRI characteristics suggesting inflammation, or detection of serum and/or CSF neural autoantibody⁷ (figure 1). Demographic, clinical (seizure semiology, course, and associated symptoms), autoimmune serology, type of AED and immunotherapy used, EEG and radiologic characteristics, and treatment outcomes were reviewed.

Baseline seizure frequency was determined by reviewing the seizure frequency stated in the clinical record prior to initiation of treatment and categorized as daily (>1 seizure per day), weekly (>1 seizure per week but not daily), or monthly (>1 seizure per month but not weekly). Response to AED with and without immunotherapy was determined by review of the record documenting course following treatment initiation.

Statistical analysis. Data were expressed as mean, range, and SD for continuous variables, and counts (percentages) for

Figure 1 Flowchart showing methodology of study design



AANA-1 = antineuronal nuclear antibody-1; AED = antiepileptic drug; EMR = electronic medical record; G-ACR = ganglionic acetylcholine receptor; GAD65 = glutamic acid decarboxylase 65; NMDAR = NMDA receptor; SSA = Sjögren's-syndrome-related antigen A; TPO = thyroid peroxidase; VGCC = voltage-gated calcium channel; VGKC-complex = voltage-gated potassium channel-complex.

categorical variables. We compared treatment response by antibody type (VGKC-complex antibodies vs GAD65 vs antibody negative) using the Fisher exact test. All analyses were performed using SAS software (version 9.3). All statistical tests were 2 sided, and $p < 0.05$ was considered statistically significant.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Mayo Clinic Institutional Review Board, and all patients consented to the use of their medical records for research purposes.

RESULTS Clinical characteristics. Patients age ranged from 10 to 87 years (mean age 41.3 years); 26 (52%) were men. The mean age at onset was 41 years. The median follow-up period was 18 months (range 3–44 months). Seizure types were focal seizures with and without loss of awareness, faciobrachial dystonic seizures, epilepsy partialis continua, and generalized tonic-clonic seizures with/without status. EEG was abnormal with interictal discharges or documented seizure activity in the majority of cases. MRI data were abnormal in 23 patients. Brain PET CT was performed in 4 patients, and it was abnormal in each. Summary of clinical characteristics of the 50 patients is provided in table 1.

Autoantibody evaluation. Neural autoantibodies were identified in 38 patients (76%), of which 26 had antibodies targeting plasma membrane proteins: VGKC-complex antibody (n = 17) (LG11 [11], CASPR2 [1], and double negative [5]); ganglionic acetylcholine receptor (G-AChR) (n = 5); NMDA receptor (n = 3); P/Q-type calcium channel (n = 1), and 12 had antibodies targeting cytoplasmic or nuclear proteins: P GAD65 (n = 10), ANNA-1 (n = 1), and ANNA-2 (n = 1). Three patients (6%) had non-neuronal antibodies (thyroid peroxidase [TPO], Ant-Ro, and anti-dsDNA), and nine patients (18%) were autoantibody negative.

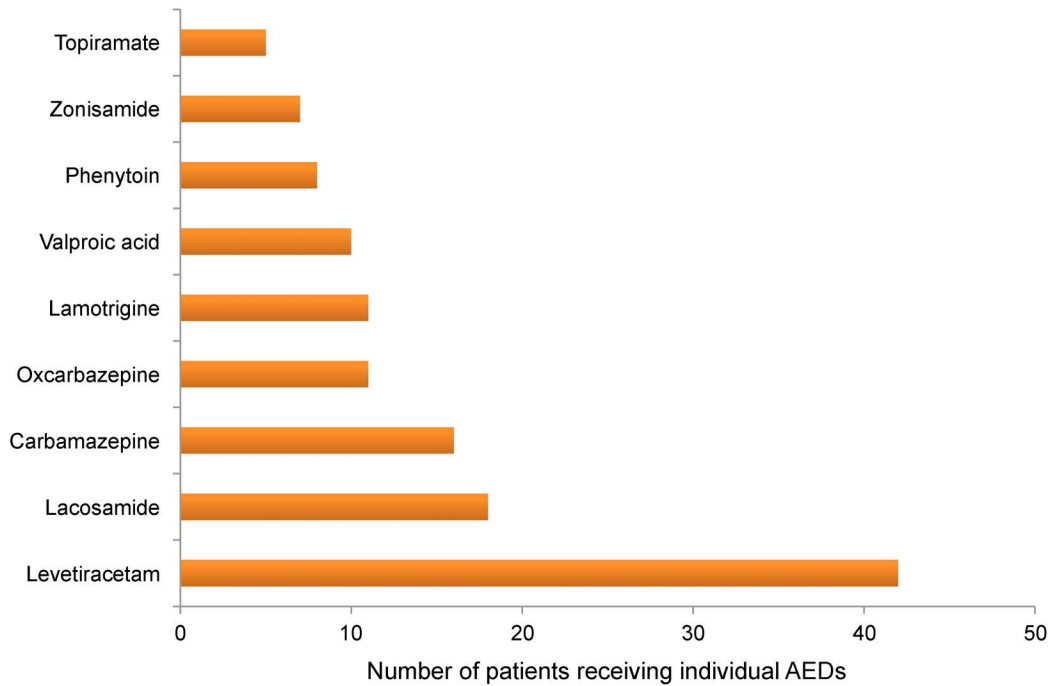
Treatments and response. The majority (n = 43, 86%) received at least 1 form of immunotherapy in combination with AEDs, while the remainder received AEDs alone. The median number of AEDs used was 2 (range 1–6). Levetiracetam was the most common medication used (n = 42), followed by lacosamide (n = 18), carbamazepine (n = 16), oxcarbazepine (n = 11), lamotrigine (n = 11), and phenytoin (n = 8). Summary of AED use for the cohort is provided in figure 2. In addition, 4 patients received vagus nerve stimulation therapy, and 3 patients had unsuccessful epilepsy surgeries. The rationale for selecting one AED over the other was not clarified in the electronic medical record (EMR). Twenty-seven patients (54%) became seizure free: 18 (36%) with immunotherapy, 5 (10%) with AEDs alone, and 4 (8%) with AEDs after failing immunotherapy. Initiation of carbamazepine (n = 3) (3/16, 18.8%), lacosamide (n = 3) (3/18, 16.6%), phenytoin (n = 1) (1/8, 12.5%), or oxcarbazepine (n = 2) (2/11, 18.1%) resulted in seizure-free

Table 1 Summary of clinical characteristics of 50 patients with suspected AE

Characteristics	
Sex, n (%)	
Male	26 (52)
Female	24 (48)
Mean age at onset, y	41
Seizure type, n (%)	
Focal seizures with/without loss of awareness	33 (66)
Faciobrachial dystonic seizures	4 (8)
Epilepsia partialis continua	4 (8)
GTCs with/without status	14 (28)
Others (absence, myoclonic, hypermotor, and atonic)	5 (10)
No. of AEDs, n (%)	
≤1	19 (38)
≥2	31 (62)
Seizure frequency, n (%)	
≥1/day	26 (52)
≥1/week	9 (18)
≥1/month	5 (10)
<1/month	10 (20)
Seizure freedom, n (%)	
With immunotherapy (IVMP and/or IVIG)	19 (38)
AEDs alone	5 (10)
AEDs after failing immunotherapy	4 (8)
Others (MAD, VNS, etc)	2 (4)
Neuronal autoantibody status, n (%)	
Neuronal autoantibody	38 (76)
VGKC-complex	17 (34)
GAD65	10 (20)
G-AChR	5 (10)
NMDAR	3 (6)
P/Q-type calcium channel	1 (2)
ANNA-1	1 (2)
ANNA-2	1 (2)
Others (TPO, Ant-Ro, anti-dsDNA)	3 (6)
Negative	9 (18)
MRI with probable inflammatory changes, n (%)	
EEG with IEDs or documented seizure activity, n (%)	38 (76)

Abbreviations: AANA-1 = antineuronal nuclear antibody-1; AANA-2 = antineuronal nuclear antibody-2; G-AChR = ganglionic acetylcholine receptor; AE = autoimmune epilepsy; AED = antiepileptic drug; GAD65 = glutamic acid decarboxylase 65; GTC = generalized tonic-clonic seizure; IED = interictal discharge; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; MAD = modified Atkins diet; NMDAR = NMDA receptor; TPO = thyroid peroxidase; VGKC-complex = voltage-gated potassium channel-complex; VNS = vagus nerve stimulation.

Figure 2 Pattern of AED use in 50 patients with suspected AE



AE = autoimmune epilepsy; AED = antiepileptic drug.

outcomes, while none of the patients became seizure free with levetiracetam ($n = 0$) (0/42, 0%). The timing of therapeutic response to AEDs (i.e., cessation of clinical seizures) was immediate: within 24 hours in 1 patient, within 1 week in 2, within 2 weeks in 3, and within 4 weeks in the remainder.

Among those who responded to AED therapy, 4 were VGKC-complex antibody positive (1 LGI1, 1 CASPR2, and 2 double negative), 1 was GAD65 antibody positive, 1 was AChR antibody positive, 1 was TPO antibody positive, and 2 were autoantibody negative. Regardless of the type of therapy, VGKC-complex antibody-positive patients were more likely to become seizure free compared with GAD65-positive and autoantibody-negative cases (12/17 vs 2/10 vs 2/9 respectively, $p < 0.05$). Specifically, of the VGKC-complex antibody patients who became seizure free, 4 responded to AEDs (25%), while the remainder became seizure free with immunotherapy (75%). One patient with GAD65 ab-associated AE responded to carbamazepine, while the other became seizure free with immunotherapy. Two of the autoantibody-negative cases responded to AEDs (carbamazepine), and 2 became seizure free with immunotherapy. Details of patients who responded to AEDs alone or after failure of immunotherapy are summarized in table 2 and figure 3.

DISCUSSION Although the seizures in AE are often considered to be medication resistant, and

immunotherapy is often the focus of management,⁷ this study suggests that in select cases AEDs alone may confer seizure freedom.

Of interest in our study, 9 patients became seizure free after the initiation of AEDs with sodium channel blocking properties⁷ (carbamazepine, $n = 3$; oxcarbazepine, $n = 2$; lacosamide alone, $n = 3$, or with phenytoin, $n = 1$). The response to AEDs was seen within 2–4 weeks of the initiation of therapy in all patients. In a few patients, AEDs alone were effective in controlling seizures. However, improvement of cognitive symptoms and other manifestations of autoimmune encephalitis in most patients requires immunotherapy.⁷ It is conceivable that these therapeutic responses could be secondary to immunomodulatory properties of these medications.^{4–6} For example, carbamazepine has been shown to reduce levels of proinflammatory cytokines IL-1 β and TNF α in the hippocampus of rats⁴ and inhibits the development of different types of inflammation through dose-dependent reduction of prostaglandin E2 and substance P.⁵ Carbamazepine and oxcarbazepine have also been shown to decrease serum levels of IL-1 and IL-2 in healthy subjects.⁵ Although disruption of blood-brain barrier permeability has been suggested as a possible pathway for cytokines influencing seizures and epilepsy,⁸ the exact role of cytokines in human epilepsy is complex and not yet completely elucidated. Moreover, whether there are unique aspects of the

Table 2 Clinical characteristics of patients who become seizure free with AED therapy

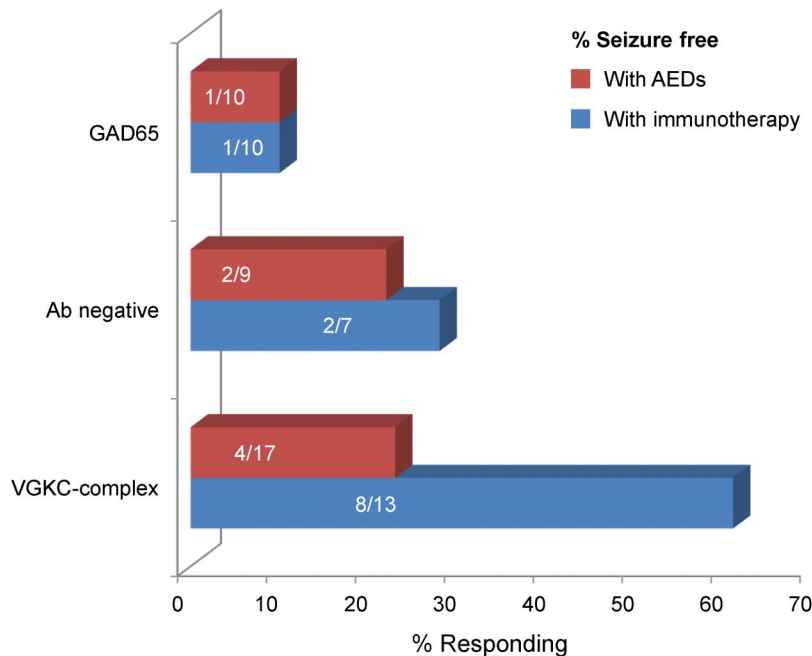
Sex/age, y	Presenting symptoms	AEDs previously tried	AEDs responded to	EEG abnormalities	MRI abnormalities	Autoantibody profile (titer)	Immunotherapy tried	Duration of seizure freedom, mo
M/58	Focal dyscognitive seizures + cognitive challenges	Levetiracetam	Oxcarbazepine	Temporal IEDs	Unremarkable	VGKC-complex, LGI1 +ve (0.33 nm/L)	None	48
F/61	Focal dyscognitive seizures + cognitive impairment	Topiramate	Oxcarbazepine	Temporal IEDs	Swollen left amygdala	VGKC-complex, LGI1, and CASPR2 -ve (0.15 nm/L)	IVMP (later for cognitive impairment)	16
M/70	Focal seizures with GTCs + cognitive impairment	Levetiracetam	Carbamazepine	Multifocal IEDs	R > L hippocampal atrophy	VGKC-complex, LGI1, and CASPR2 -ve, (0.19 nm/L)	None	68
M/68	Focal dyscognitive seizures + subacute cognitive decline	Levetiracetam	Lacosamide	Temporal IEDs	Unremarkable	VGKC-complex, CASPR2 +ve (0.10 nm/L)	None	7
M/68	Focal dyscognitive seizures + memory impairment	Phenytoin (low dose)	Phenytoin + lacosamide	Temporal IEDs	Mild diffuse cerebral atrophy	G-AChR (0.64 nm/L)	IVIG then IVMP	30
F/67	Focal dyscognitive seizures + cognitive impairment	Levetiracetam	Carbamazepine	Temporal IEDs	Unremarkable	GAD65, 404 nm/L	IVIG	37
M/63	Focal seizures + cognitive impairment	Carbamazepine (rash)	Lacosamide	Temporal slowing	T2 signal change, amygdala	TPO, 21 IU/mL	IVMP (later for cognitive impairment)	11
F/63	Focal dyscognitive seizures + personality change + dysphasia	Levetiracetam + phenytoin (rash)	Lacosamide	Temporal IEDs	Lt temporal T2 signal change + enhancement	Negative	None	20
M/59	Refractory focal seizures	Levetiracetam + lamotrigine (rash)	Carbamazepine	Temporal IEDs	T2 signal hyperintensity + swollen amygdala	Negative	IVMP	24

Abbreviations: AED = antiepileptic drug; CASPR2 = contactin-associated protein-2; F = female; G-AChR = ganglionic acetylcholine receptor; GAD65 = glutamic acid decarboxylase 65; GTC = generalized tonic-clonic seizure; IED = interictal discharge; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; LGI1 = leucine-rich inactivated 1 protein; M = male; TPO = thyroid peroxidase; VGKC-complex = voltage-gated potassium channel-complex.

pathophysiology of seizure onset in these patients which make them more susceptible to sodium channel blockage is not known. The observed response could also be due to the effectiveness of sodium channel blockers in focal onset epilepsy which is seen in 66% of patients in our cohort. Of note, while AED responders responded to sodium channel blockers, no patient responded to lamotrigine, which also has sodium channel properties.⁹ Therefore, if there is a unique responsivity of seizures in these patients to this class of medications, the response may not be uniform throughout the entire class. Studies are needed to elucidate whether any differential efficacy is based on their effect on seizure mechanisms or immunomodulatory properties.

Regardless of the type of therapy, VGKC-complex antibody-positive patients were more likely to become seizure free compared with GAD65-positive and autoimmune antibody-negative cases (figure 2). This is consistent with previous observations of superior immunotherapy response in patients with neural surface-related autoantibody-mediated encephalitides as compared to those associated with intracellular antigen autoantibodies.^{1,7,10} Of note, among the patients who responded to AEDs in our cohort, the majority were VGKC-complex antibody positive (1 LGI1 positive; 1 CASPR2 positive, and 2 double negative). Two of these responded to oxcarbazepine, one to lacosamide, and the other to carbamazepine (figure 1). Indeed, sodium-channel blocking agents such as carbamazepine and phenytoin have been successfully used to treat autoimmune VGK channelopathies such as neuro-myotonia¹¹ and episodic ataxia type 1.¹² These agents act by reducing neuronal repetitive firing through interaction with voltage-gated sodium channels.^{11,12} Perhaps, the observed favorable response of these agents in VGKC-complex ab-associated AE is attributable to this mechanism. In our series, one patient with GAD65 ab-associated AE became seizure free with carbamazepine after failing immunotherapy. This is in contrast to a similar report that found lack of AED response in patients with GAD65 antibody-positive AE following which it was postulated that GAD65 ab-associated AEs are intractable to AEDs.¹³ Regardless of the type of therapy, 4/9 (44.4%) autoantibody-negative patients become seizure free, 2 with AEDs (one with lacosamide and the other with carbamazepine after failing immunotherapy), while the other two responded to immunotherapy. Others have noted the potential for response in patients with seronegative AE to antiepileptic medication and immunotherapy.¹⁴

Figure 3 Response to therapy by antibody status



The number of patients who responded per the total number of patients receiving individual therapy is provided in each bar. Ab negative = negative to antibody testing (n = 9); AED = antiepileptic drug; GAD65 = glutamic acid decarboxylase 65 (n = 10); VGKC-complex = voltage-gated potassium channel-complex (n = 17).

The rationale for selecting one AED over the other was not clarified in the EMR of our cohort. Levetiracetam was the most common used drug (42/50, figure 2); however, none of the patients in our series were rendered seizure free by this medication (0%). This finding is in contrast to previous reports suggesting that levetiracetam may have, at least in part, anti-inflammatory properties.³ The reason for the prevalent use of levetiracetam in our series is likely due to its ease of dosing and lack of drug-drug interactions.⁹ Certainly, AEDs with enzyme induction properties such as carbamazepine and phenytoin could alter the pharmacokinetics of immunosuppressive therapies and other agents used in these patients.⁹ Perhaps, newer AEDs with sodium channel blocking properties and more favorable pharmacokinetic profiles (such as oxcarbazepine and lacosamide) could be considered in this patient population. It is also imperative to monitor for hyponatremia (e.g., oxcarbazepine and carbamazepine) and allergic cutaneous reactions (e.g., carbamazepine and phenytoin), as these have been shown to occur at high rate in patients with VGKC-complex antibody.¹⁵ Prospective studies are needed to clarify AED selection and to elucidate their immunomodulatory properties in AE.

There are several limitations to our study. First, data collection for this retrospective study was

based on the extraction of relevant patient information from EMRs. The lack of control group and the possible confounder of concomitant immunotherapy should also be acknowledged. In addition, selection bias could be present due to the tertiary nature of these patients. Finally, seizure quantification is only based on verbal report, thus recall bias could result in the event of amnesic seizures, and related to concurrent cognitive dysfunction that may have been present in a significant proportion of our cohort. Prospective studies are needed to clarify whether there is an optimal AED selection for AE. As the awareness of AE increases, finding effective strategies for seizure control is crucial.

AUTHOR CONTRIBUTIONS

Study concept and design: Dr. Feyissa and Dr. Britton. Acquisition of data: Dr. Feyissa, Dr. Lopez, and Dr. Britton. Drafting of the manuscript: Dr. Feyissa and Dr. Lopez. Critical revision of the manuscript for important intellectual content: Dr. Feyissa and Dr. Britton.

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DISCLOSURE

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