Autoimmune Epilepsy

Clinical Characteristics and Response to Immunotherapy

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Objective: To describe clinical characteristics and immunotherapy responses in patients with autoimmune epilepsy.

Design: Observational, retrospective case series.

Setting: Mayo Clinic Health System.

Patients: Thirty-two patients with an exclusive (n=11) or predominant (n=21) seizure presentation in whom an autoimmune etiology was suspected (on the basis of neural autoantibody [91%], inflammatory cerebrospinal fluid [31%], or magnetic resonance imaging suggesting inflammation [63%]) were studied. All had partial seizures: 81% had failed treatment with 2 or more antiepileptic drugs and had daily seizures and 38% had seizure semiologies that were multifocal or changed with time. Head magnetic resonance imaging was normal in 15 (47%) at onset. Electroencephalogram abnormalities included interictal epileptiform discharges in 20; electrographic seizures in 15; and focal slowing in 13. Neural autoantibodies included voltage-gated potassium channel complex antibody–positive patients reported initial or lasting benefit (P<.05). One voltage-gated potassium channel complex antibody–positive patient was seizure free after thyroid cancer resection; another responded to antiepileptic drug change alone.

Conclusion: When clinical and serological clues suggest an autoimmune basis for medically intractable epilepsy, early-initiated immunotherapy may improve seizure outcome.


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strongly correlate with clinical seizures include N-methyl-D-aspartate (NMDA), γ-aminobutyric acid B, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

Accumulating data support an autoimmune basis in patients with AED-resistant seizures. Including those lacking a typical “limbic encephalitis” phenotype. Identification of an immune basis is important because adjunctive immunotherapy may slow, halt, or even reverse the epileptogenic process in these patients. In a cohort study, autoimmune antibodies were detected in 14% of patients with epilepsy. This study, along with several case reports and series, suggested a potential benefit of immunotherapy in improving seizure control. Herein, we review the clinical characteristics and responses to immunotherapy for patients with suspected autoimmune epilepsy, evaluated jointly in an Autoimmune Neurology Clinic and Epilepsy Clinic, whose sole or predominant presenting symptom was recurrent, uncontrolled seizures.

With approval of the Mayo Clinic institutional review board, we searched the Mayo Clinic computerized diagnostic index to identify patients who were evaluated in both the Autoimmune Neurology Clinic and Epilepsy Clinic between January 1, 2005, and December 31, 2010, whose evaluations led to a diagnosis of autoimmune epilepsy. Autoimmune epilepsy was defined as (1) epilepsy as the exclusive (n=11) or predominant (n=21) presenting concern and (2) autoimmune pathogenesis suspected by the treating physicians based on detection of a neural autoantibody, inflammatory cerebrospinal fluid (CSF) (leukocytosis or CSF-exclusive oligoclonal immunoglobulin bands), or magnetic resonance imaging (MRI) characteristics suggesting inflammation (T2 hyperintensities, contrast enhancement on gadolinium studies, and/or restricted diffusion).

Demographic and clinical characteristics (seizure semiology, clinical course, and associated symptoms) were recorded. Head MRIs and whole-body radiolabeled fluorodeoxyglucose positron emission tomography (FDG-PET) scans were reviewed by at least 2 investigators (A.M.L.Q., A.L.K., and R.E.W.) blinded to the clinical data (one, a neuroradiologist). The electroencephalogram (EEG) studies were scalp recordings acquired via electrodes applied using the international 10-20 system for electrode placement. All routine EEGs comprised 2 1-channel and all prolonged 30-channel digital EEG recordings. Longitudinal and transverse bipolar, Cz and ear/mastoid referential, and Laplacian montages were used as indicated to optimize seizure detection and localization. Results of neural autoantibody screening were recorded. A composite substrate of mouse cerebellum, midbrain, stomach, and kidney was used in a standardized indirect immunofluorescence assay to detect the following neuronal and glial nuclear and cytoplasmic IgG autoantibodies: ANNA types 1 (anti-Hu), 2 (anti-Ri), and 3; Purkinje cell cytoplasmic autoantibodies types 1 (anti-Yo), 2, and Tr; CRMP-5; amphiphysin; and antiglia/neuronal nuclear antibody type 1. In-house assays included radioimmunoprecipitation to detect antibodies reactive with cation channel complexes (neuronal voltage-gated calcium channels [P/Q type and N type], VGKC complex, nicotinic acetylcholine receptors of skeletal muscle and autonomic ganglionic types) and GAD65, enzyme-linked immunosorbent (sketal muscle striational antibodies) and recombinant Western blot (CRMP-5–IgG). Frequencies of these neural autoantibodies in healthy controls (Table 1, footnote) were previously reported. Ma/Ta antibodies were identified via recombinant Western blot (Athena Diagnostics).

Supplementary immunofluorescence assays were performed on sections of mouse cerebral cortex, hippocampus, and thalamus to detect synapse-reactive IgG autoantibodies specific for NMDA, AMPA, and γ-aminobutyric acid B receptors. N-methyl-D-aspartate receptor seropositivity was confirmed molecularly by immunofluorescence on HEK293 cells transfected with NMDA receptor complementary DNA (product of EUROIMMUN). Sera positive for VGKC complex antibodies by radioimmunoprecipitation were analyzed further for IgGs specific for leucine-rich, glioma-inactivated 1 (Lgi1) or contactin-associated proteinlike 2 (Caspr2) using HEK293 cells transfected with Lgi1 or Caspr2 complementary DNA (product of EUROIMMUN). These proteins coprecipitate with Kv1 VGKC complexes solubilized from mammalian brain membranes and ligated with iodine 125–labeled α-dendrotoxin. All sera tested in 126 healthy controls were negative for VGKC complex, Lgi1, or Caspr2 autoantibodies.

Response to immunotherapy was categorized on the basis of physician and patient reports of seizure freedom, seizure improvement (reduction in seizure frequency and severity), or no change.

Data were expressed as median (range and interquartile range) for continuous variables and counts (percentages) for categorical variables. Differences between responders (seizure freedom or improvement) and nonresponders were compared using an unpaired t test, analysis of variance, and Wilcoxon rank sum tests for continuous measures and χ² and Fisher exact tests for categorical variables.

CLINICAL CHARACTERISTICS

Clinical, radiological, EEG, autoimmune serologic values, and immunotherapeutic outcomes for 32 patients are presented in Table 1 and Table 2. All presented with recurrent seizures. Fifty-nine percent were female. Median seizure onset age was 56.0 years (range, 5-79 years). Median history of seizure activity prior to Mayo Clinic presentation was 5 months (range, 3 weeks to 12 years). An autoimmune basis was suspected based on detection of a neural autoantibody (91%), inflammatory CSF (leukocytosis or CSF-exclusive oligoclonal immunoglobulin bands) (31%), or MRI characteristics suggesting inflammation (63%).

SEIZURE AND EEG CHARACTERISTICS

Partial seizures were the predominant clinical presentation: simple partial and/or auras, 27 of 32 (84%); complex partial, 26 of 32 (81%); and secondary generalized tonic-clonic, 17 of 32 (53%). Seizure semiologies were variable or changed over time in 12 patients (38%). Most patients (81%) had received 2 or more AEDs at presentation (median, 3 AEDs), yet seizures were frequent: 26 (81%) had daily seizures; the remaining had at least 1 seizure per month.

Two patients had undergone epilepsy surgery without seizure benefit elsewhere (anterior temporal lobectomy plus amygdalohippocampectomy and frontal corticectomy, patients 5 and 14, respectively); none had a neoplasm. Perivascular chronic inflammatory cell infiltrates (mainly T lymphocytes) were noted on histopathology review at
<table>
<thead>
<tr>
<th>Patient/ Sex/ Age, y</th>
<th>Epilepsy Duration, mo</th>
<th>Seizure Type/Semiology</th>
<th>Cognitive</th>
<th>EEG Abnormalities (Region)</th>
<th>MRI Probable Inflammatory Changesb</th>
<th>CSF Abnormality (Value)c</th>
<th>Autoantibody Profile (Titer)d,e</th>
<th>IXT (Frequency, No. of Treatments/ Duration)</th>
<th>Post-ITX Seizure Outcome and Antibody Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/61 2.75</td>
<td>2/Weekly</td>
<td>SPS: bilateral independent facial clonus; auras: flushing, diffuse tingling; CPS (variable semiologies): bicycling, oral automatisms, unilateral limb posturing; GTCf</td>
<td>Cognitive</td>
<td>2/Daily IED (fronto-temporal)</td>
<td>L medial temporal (Gad+)(DWI+)</td>
<td>Normal</td>
<td>VGKC complex (2.58), Lg1+, Caspr2–, TPO (12.2)</td>
<td>IVlg (daily, 3; weekly, 5); IVMP (daily, 5; weekly, 4); PLEX (7); MMF (4 mo; ongoing)</td>
<td>Seizure freedom (9 mo)</td>
</tr>
<tr>
<td>2/M/61 10</td>
<td>2/Monthly</td>
<td>Auras: déjà vu; CPS: unresponsive staring</td>
<td>Cognitive; personality</td>
<td>3/Daily IED (temporal), IA (multi-temporal and extratemporal); FS (temporal), generalized slowing</td>
<td>R temporal posterior-lateral cortex (Gad–)(DWI–)</td>
<td>OCB (4)</td>
<td>CRMP–S</td>
<td>IVMP (daily, 5); oral dexa (5 d monthly for 24 mo); repeated cycles of IVMP owing to relapses (&gt;2); MMF (2.5 y; ongoing)</td>
<td>Seizure improvement; post-ITX CRMP–S-ongoing</td>
</tr>
<tr>
<td>3/F/16 1.5</td>
<td>3/Daily</td>
<td>Changed over time; SPS (variable semiologies); leg jerking, UE jerking; EPC: continuous low amplitude R finger a facial jerking; CPS: unresponsive staring; rare GTCf</td>
<td>Cognitive; personality</td>
<td>3/Daily IED (temporal), IA (multi-temporal and extratemporal); FS (temporal), generalized slowing</td>
<td>Post-temporal lobectomy gliosis; R MTS</td>
<td>WBC count (7), protein level (68)</td>
<td>VGKC complex (1.2), Lg1+, Caspr2–</td>
<td>IVMP (daily, 5); IVlg (daily, 3; weekly, 9; monthly, 10); every 2 mo, 3; MMF (4.5 y)</td>
<td>Seizure freedom (15 mo; post-ITX CRMP–S-ongoing)</td>
</tr>
<tr>
<td>4/M/64h 11.5</td>
<td>3/Monthly</td>
<td>Changed over time; auras and CPS (variable); diffuse hot sensation, auditory hallucinations; GTCf</td>
<td>Cognitive</td>
<td>3/Monthly IED (temporal), IA (temporal), FS (temporal), generalized slowing</td>
<td>Post-temporal lobectomy gliosis; R MTS</td>
<td>WBC count (7), protein level (68)</td>
<td>VGKC complex (1.2), Lg1+, Caspr2–</td>
<td>IVMP (daily, 5); IVlg (daily, 3; weekly, 9; monthly, 10); every 2 mo, 3; MMF (4.5 y)</td>
<td>Seizure freedom (48 mo; post-ITX VGKC complex, 0.14)</td>
</tr>
<tr>
<td>6/F/67g 5</td>
<td>1/Monthly</td>
<td>GTC out of sleep (no reported SPS or CPS)</td>
<td>Cognitive</td>
<td>1/Monthly IED (temporal), generalized slowing</td>
<td>Not done</td>
<td>VGKC complex (3.5), Lg1+, Caspr2–</td>
<td>No ITX; seizures continued with first AED; subsequent change to second AED, with seizure freedom thereafter; eventually stopped taking all AEDs</td>
<td>IVMP (daily, 5; S &lt; 2; monthly, 8); MMF (17 mo)</td>
<td>Seizure freedom (42 mo)</td>
</tr>
<tr>
<td>7/F/57 2.5</td>
<td>2/Monthly</td>
<td>EPC: occipital origin; unilateral visual hallucinations, intermittent unilateral UE stiffness; CPS: intermittent confusion; GTCf</td>
<td>Cognitive</td>
<td>2/Monthly IED (temporal and extratemporal), IA (extra-temporal; EPC), FS (temporal), generalized slowing</td>
<td>R medial temporal, R thalamus, R occipital (Gad–)(DWI–), R MTS</td>
<td>WBC count (19), protein level (58)</td>
<td>None, TPO (49), RF</td>
<td>IVMP (daily, 5; S &lt; 2; monthly, 8); MMF (17 mo)</td>
<td>Seizure freedom (42 mo)</td>
</tr>
<tr>
<td>8/F/57g 5</td>
<td>8/Daily</td>
<td>Auras: unilateral visual hallucinations and nausea; CPS: unresponsive staring, unilateral facial and UE posturing; GTCf</td>
<td>Cognitive</td>
<td>8/Daily Generalized slowing</td>
<td>WBC count (7), protein level (61)</td>
<td>VGKC complex (4.21), Lg1+, Caspr2–, TPO (61), RF</td>
<td>IVMP (daily, 5; fortnightly, 4; monthly, 2; every 2 mo, 2; MMF (3 y 4 mo)</td>
<td>Seizure freedom (48 mo; post-ITX VGKC complex, 0.39)</td>
<td>(Continued)</td>
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</table>
Table 1. Clinical Characteristics* (continued)

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>Epilepsy Duration, mo</th>
<th>Seizure Type/Semiology</th>
<th>Neurologic Abnormalities</th>
<th>MRI Probable Inflammatory Changes</th>
<th>CSF Abnormality (Value)</th>
<th>Autoantibody Profile/Titer</th>
<th>ITX (Frequency, No. of Treatments/Duration)</th>
<th>Post-ITX Seizure Outcome and Antibody Titer</th>
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</thead>
<tbody>
<tr>
<td>9/2/35 4</td>
<td>SPS: intermittent unilateral LE paresthesia and posturing; GTC</td>
<td>3/Daily Normal</td>
<td>Normal</td>
<td>Normal (GAD65 3.38)</td>
<td>IVlg (daily, 4 × 2; twice weekly, 2)</td>
<td>Seizure freedom (10 mo); post-ITX GAD65, 2.96</td>
<td></td>
<td></td>
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<tr>
<td>10/2/48 12</td>
<td>Aura: olfactory and gustatory hallucination; CPS: unresponsive staring</td>
<td>4/Daily IED (temporal, FS (temporal), IA (extra-temporal, EPC))</td>
<td>L, medial temporal (Gad−) (DWI−), R MTS</td>
<td>Normal (GAD65 4.86, TPO &lt; 650)</td>
<td>Lost to follow-up</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11/5/79 3.75</td>
<td>EPC: unilateral UE and LE clonic jerking</td>
<td>0/Daily IED (extra-temporal), L frontal (Gad−) (DWI−), Protein level (62), OCB (5)</td>
<td>None</td>
<td>IVMP (daily, 5; weekly, 3); CMP (monthly, 11)</td>
<td>No response</td>
<td></td>
<td></td>
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<tr>
<td>12/5/73* 7</td>
<td>Aura: rising abdominal sensation; CPS: unresponsive staring</td>
<td>3/Daily FS (temporal, generalized slowing)</td>
<td>R, medial temporal (Gad−) (DWI−), R MTS</td>
<td>Normal (VGKC complex (0.62), Lg1+, Caspr2−, TPO &lt; 85)</td>
<td>IVMP (daily, 3; weekly, 2; fortnightly, 6; every 3 wk, 3; monthly, 2); Pred (4 mo)</td>
<td>Seizure freedom (13 mo); post-ITX VGKC complex, 0.24</td>
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<tr>
<td>13/5/39 36</td>
<td>Changed over time; aura: multiple daily episodes of “wave” down R side with unilateral paresthesia, olfactory hallucinosis in past; SPS: unilateral L UE and LE jerking and pulling a L facial; CPS: unresponsive staring; GTC</td>
<td>6/Daily Normal</td>
<td>R, medial temporal (Gad−) (DWI−), R MTS</td>
<td>Normal (VGKC complex (0.62), Lg1+, Caspr2−, ANA, EPO)</td>
<td>IVMP (daily, 3; weekly, 12; fortnightly, 6; every 3 wk, 2; weekly ongoing and tapering); MMF (3 mo, ongoing); rituximab for relapses of wavelike spells (1000 mg x2)</td>
<td>Seizure improvement; post-ITX VGKC complex, 0.00</td>
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<tr>
<td>14/5/24 96</td>
<td>Aura: jamais vu, fear; CPS: unresponsive staring with oral and limb automatisms; GTC</td>
<td>7/Monthly IED (temporal and extratemporal), FS (extra-temporal), generalized slowing</td>
<td>Post-L; frontal leucoencephalopathy changes, bilateral MTS</td>
<td>Protein level (43)</td>
<td>GAD65 (608), TPO &lt; 165.5, EPO</td>
<td>IVMP (daily, 5) (developed avascular necrosis of hip; relapsed postoperatively); IVlg (daily, 3; fortnightly, 6; every 3 wk, 2); IVMP (daily, 3; fortnightly, 4; daily, 3; every 3 wk, 2); MMF (2 y, ongoing)</td>
<td>Seizure freedom (6 mo)</td>
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<tr>
<td>15/6/5 22</td>
<td>SPS (variable): unilateral UE jerking, unilateral and bilateral “jolt” sensation; aura: migrating paresthesias on scalp; CPS: unresponsive staring; GTC</td>
<td>3/Daily FS (temporal)</td>
<td>L, medial temporal (Gad−), bilateral MTS</td>
<td>Normal</td>
<td>VGKC complex (0.27), Lg1+, Caspr2−, TPO &lt; 85</td>
<td>IVMP (daily, 3; weekly, 8); MMF (1 mo, ongoing)</td>
<td>Seizure freedom (3 mo)</td>
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<thead>
<tr>
<th>Patient/SEX/AGE, y</th>
<th>Epilepsy Type</th>
<th>Seizure Duration, mo</th>
<th>Epilepsy Duration, mo</th>
<th>Seizure Type/Semiology</th>
<th>Neurologic Association</th>
<th>No. of AEDs/Seizure Abnormalities</th>
<th>EEG Abnormalities (Region)</th>
<th>MRI Probable Inflammatory Changes</th>
<th>CSF Abnormality (Value)</th>
<th>Autoantibody Profile (Titer)</th>
<th>ITX (Frequency, No. of Treatments/Duration)</th>
<th>Post-ITX Seizure Outcome and Antibody Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/M/54</td>
<td>3</td>
<td>Daily</td>
<td>IED (extra-temporal), IA (extra-temporal)</td>
<td>L temporal lobe (DWI+), L caudate and putamen (Gad−), L MTS</td>
<td>Protein level (94)</td>
<td>VGKC complex (5.35), Lgi1−, Caspr2−</td>
<td>IVMP (daily, 5; weekly, 6; fortnightly, 6; every 3 wk, 2; fortnightly, 4; every 3 wk, 4; monthly, 6)</td>
<td>Cognitive; personality</td>
<td>Seizure freedom (3 mo); post-ITX VGKC complex, 0.00</td>
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<tr>
<td>17/F/60</td>
<td>3</td>
<td>Daily</td>
<td>IED (temporal), IA (temporal)</td>
<td>R temporal lobe (Gad+) (DWI−)</td>
<td>Normal</td>
<td>GAD65 (0.28), VGKC complex (5.25), Lgi1−, Caspr2−, TPO (52.9)</td>
<td>IVIg (reducing frequency over 1.5 y, ongoing)</td>
<td>Cognitive; personality; psychiatric</td>
<td>Seizure freedom (17 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/M/53</td>
<td>10.5</td>
<td>Daily</td>
<td>IED (temporal), IA (temporal), FS (temporal and extra-temporal)</td>
<td>L temporal lobe (Gad−) (DWI−), bilateral MTS</td>
<td>Normal</td>
<td>VGKC complex (0.28), Lgi1−, Caspr2−</td>
<td>IVMP (daily, 5; weekly, 8; fortnightly, 4; every 3 wk, 3; monthly, 4; every 3 wk, 4; monthly, 10); MF (22 mo, ongoing)</td>
<td>Cognitive; personality; psychiatric</td>
<td>Seizure improvement (initial seizure freedom, 21 mo, before relapse with new seizure semiology responding to increasing AED); post-ITX VGKC complex, 0.00</td>
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<tr>
<td>19/M/60</td>
<td>36</td>
<td>Daily</td>
<td>Temporal EA</td>
<td>L temporal lobe (Gad−) (DWI−)</td>
<td>Protein level (74)</td>
<td>Ganglioside acetylcholine receptor (0.08), Rf</td>
<td>IVMP (daily, 5; weekly, 5); IVIg (daily, 3; weekly, 5)</td>
<td>Cognitive; psychiatric</td>
<td>No response (subsequently responded when lacosamide started)</td>
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<tr>
<td>20/F/17</td>
<td>144</td>
<td>Weekly</td>
<td>IED (temporal), IA (temporal), FS (temporal)</td>
<td>R temporal lobe (Gad−) (DWI−)</td>
<td>Normal</td>
<td>GAD65 (197), TPO (871)</td>
<td>Advised but did not return for follow-up</td>
<td>Cognitive; psychiatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21/M/62</td>
<td>48</td>
<td>Daily</td>
<td>EA (temporal)</td>
<td>R temporal lobe (Gad−) (DWI−)</td>
<td>Normal</td>
<td>None</td>
<td>IVMP (daily, 3; weekly, 6); IVIg (daily, 3; weekly, 6; fortnightly, 4; every 3 wk, 4; monthly, 4)</td>
<td>Personality; psychiatric</td>
<td>Seizure freedom (12 mo)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>22/F/53</td>
<td>84</td>
<td>Daily</td>
<td>IED (temporal), IA (temporal)</td>
<td>R temporal lobe (temporal and insula (Gad−) (DWI−), R MTS</td>
<td>Normal</td>
<td>MAb1, MAb2, TPO (60.2)</td>
<td>IVMP (daily, 3; weekly, 6; fortnightly, 3); AZA (5 mo); CMB (monthly, 4 and ongoing for 2 more months)</td>
<td>Cognitive; personality</td>
<td>No response</td>
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</tr>
</tbody>
</table>

**OTHER NEUROPSYCHIATRIC MANIFESTATIONS**

Additional manifestations included memory and cognitive difficulties, 20 (63%); personality changes, 8 (25%); and depression or anxiety, 6 (19%). Neurocognitive changes developed subsequently in 3 of 11 patients who did not have memory or affective changes at presentation (34%).
NEUROIMAGING FINDINGS

Magnetic resonance imaging brain scans were available for review in all patients (Figure and eTable 2). Fifteen (47%) had normal MRIs at the time of initial seizure evaluation. Abnormalities were observed in 22 (17 at initial evaluation, 5 on follow-up imaging): probable inflammatory changes were interpreted in 20 (63%); 2 showed postsurgical changes. Among the 5 patients whose inflammatory changes were only detected on
Table 1. Clinical Characteristics (continued)

<table>
<thead>
<tr>
<th>Patient/ Sex/ Age, y</th>
<th>Epilepsy Duration, mo</th>
<th>Seizure Type/Semiology</th>
<th>Neurologic Association</th>
<th>No. of AEDs/Seizure Frequency</th>
<th>EEG Abnormalities (Region)</th>
<th>MRI Probable Inflammatory Changes</th>
<th>CSF Abnormality (Value)</th>
<th>Autoantibody Profile (Titer)</th>
<th>ITX (Frequency, No. of Treatments/ Duration)</th>
<th>Post-ITX Seizure Outcome and Antibody Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/M/71</td>
<td>1.5</td>
<td>Auras: chills head to shoulder, photoreaction; CPS: euphoria, laughter, nonverbal speech, bilateral UE jerking, confusion; GTC</td>
<td>Cognitive</td>
<td>3/Daily FS (temporal), generalized slowing</td>
<td>L, medial temporal (DWP−)</td>
<td>Protein (66) VGKC complex (0.62), LG1−, Caspr2−</td>
<td>Change of AED led to seizure resolution, but cognitive difficulties persisted; immunotherapy instituted for cognitive changes</td>
<td></td>
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</tr>
<tr>
<td>31/M/64</td>
<td>11</td>
<td>Auras/SPS (variable): shivering, surge in head or chest, tunneling of vision, olfactory hallucinations, word-finding difficulty; CPS: confused behavior; hyperventilation; GTC</td>
<td></td>
<td>3/Daily IED (temporal), IA (temporal), FS (temporal), FS (temporal and extratemporal)</td>
<td>Normal VGKC complex (0.13), LG1−, Caspr2−</td>
<td>IVMP (daily, 5) × 2 (daily, 5); PLEX (daily, 5); MMF (3 mo) × 1; ITX (daily, 3; weekly, ongoing)</td>
<td>Seizure improvement; post-ITX VGKC complex, 0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32/F/27</td>
<td>1.5</td>
<td>SPS: aphasia; GTC</td>
<td></td>
<td>5/Daily IED (temporal and extratemporal), IA (temporal and extratemporal), FS (temporal and extratemporal), generalized slowing</td>
<td>L, parietal, occipital, and frontal lobe, L, cerebellum</td>
<td>Protein level (49), WBC count (218)</td>
<td>IVMP (daily, 5) × 2 (weekly, 6 and fortnightly, 4 and ongoing); Pred (daily, tapering); rituximab started owing to subsequent clinical, aphasia, and radiological deterioration</td>
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</tbody>
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Abbreviations: AED, antiepileptic drug; ANA, antinuclear antibody; AZA, azathioprine; Caspr2: contactin-associated proteinlike 2; CMP, cyclophosphamide; CPS, complex partial seizures; CRMP-5, collapsin response-mediator protein 5; CSF, cerebrospinal fluid; dexamethasone; DWI, restricted diffusion; EEG, electroencephalography; EPC, epilepsia partialis continua; FDC, facial dysmorphia; GAD65, glutamic acid decarboxylase 65; GTC, generalized seizures; IA, ictal activity; IED, interictal epileptiform discharge; ITX, immunotherapy; IVIg, intravenous immune globulin; IVMP, intravenous methylprednisolone; L, left; LE, lower extremity; LG1, leucine-rich, glioma inactivated 1; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; MTS, medial temporal sclerosis; NMDAR, N-methyl-D-aspartate receptor; OCB, oligoclonal band; PLEX, plasma exchange; Pred, prednisolone; R, right; RF, rheumatoid factor; SPS, simple partial seizures; TPO, thyroid peroxidase; UE, upper extremity; VGKC, voltage-gated potassium channel; WBC, white blood cell; +, positive; −, negative.

aNonneurologic autoimmune disease or cancer: thyroid disease, patients 1, 7, 8, 10, 15, 25, 27, 28, and 31; celiac sprue: patients 2 and 7; diabetes mellitus, patients 4, 10, 20, 28, and 29; premature menopause, patient 9; psoriasis, patient 17; pernicious anemia, patients 25, 29, and 30; thyroid papillary cancer, patient 2; recurrence of bladder cancer, patient 4; breast cancer, patient 11; prostate cancer, patients 16 and 21; and cervical cancer, patient 27.

bPresence and location of MRI inflammatory changes, evidenced by T2-fluid-attenuated inversion recovery hyperintensities.

cUnit of measure for cell count is cells per microliter; unit of measure for protein is milligrams per deciliter. Cerebrospinal fluid reference ranges: WBC count, <4 × 10^6/L; protein, <0.35 mg/dL; and OCBs, <4.

dAutoantibodies reference range for normal values: GAD65 antibody, <0.02 nmol/L; neuronal ganglioside acetylcholine receptor antibody, <0.02 nmol/L; TPO antibody, <9 IU/mL; VGKC complex antibody, <0.02 nmol/L.

eFor the neural autoantibodies implicated in this study, a recent study showed the following frequencies of these antibodies in 161 normal healthy controls: GAD65 antibody, 0%; CRMP-5, 0%; GAD65, 2.5%; and VGKC complex, <1%.

fVideo EEG monitoring performed.

gAlso reported elsewhere.

hAlso reported elsewhere.
of the routine procedure during PET, and none were performed with concurrent EEG monitoring. Medial temporal and extratemporal hypometabolism was detected in 1 patient.

**AUTOANTIBODY PROFILES AND MALIGNANCY SCREENING**

Neural autoantibodies were identified in 29 patients (91%). Specificities were VGKC complex, 18; GAD65, 7; CRMP-5, 2; Ma (PNMA1 and PNMA2), 1; NMDA receptor, 1; and neuronal nicotinic acetylcholine receptor, ganglionic type, 1. Among the 18 patients who had VGKC complex IgG, 14 (78%) bound to Lgi1, 1 bound to Caspr2, and 3 were of unknown specificity (eFigure 1). The 3 patients who lacked detectable neural autoantibodies (patients 7, 11, and 21) had other features that supported the likelihood of autoimmune epilepsy: 2 had inflammatory CSF, all 3 had inflammatory MRI abnormalities, 2 had a personal history of cancer (1 prostate and 1 breast), and 1 had coexistent autoimmune disease (thyroid disease and celiac sprue). None had laboratory findings to indicate an infectious etiology.

The identification of a neural autoantibody led in 3 patients (patients 2, 4, and 16) to prospective detection of cancer: 2 with VGKC complex antibodies had thyroid or prostate carcinoma and 1 patient with CRMP-5 antibody had recurrent bladder cancer. Cerebrospinal fluid abnormalities were found in 19 of 30 patients (63%) evaluated: elevated leukocyte count (>5×10⁶/L), 5 patients; CSF-exclusive oligoclonal bands, 5 patients; and elevated protein level (>35 mg/dL), 17 patients.

**IMMUNOTHERAPY AND RESPONSE**

Immunotherapy was instituted in 27 of 32 patients for the treatment of persistent seizures despite AED therapy (Table 3). Initial immunotherapy comprised intravenous methylprednisolone alone (IVMP) (n = 12); intravenous immune globulin alone (IVIg) (n = 3); and combinations of IVMP, IVIg, cyclophosphamide, or plasmapheresis (n = 12). The median follow-up period was 17 months (range, 3-72 months). At last follow-up, 26 of 27 patients (96%) had improved clinically after initiation of immunotherapy. The median time from seizure onset to initiating immunotherapy was 4 months for responders and 22 months for nonresponders (P < .05). All 15 VGKC complex antibody–positive patients and 3 of 5 GAD65-seropositive patients (60%) reported benefit (P < .05 and P = .17, respectively) (eTable 3). Five responders had relapses during follow-up. With further immunotherapy and/or AED treatment, 2 eventually achieved seizure control. Their autoantibody specificities were CRMP-5, 1; GAD65, 1; and VGKC complex (Lgi1), 3. Five patients did not respond to immunotherapy. However, 2 of the 5 demonstrated subsequent improvement after AEDs were changed (patients 19 and 29).

Eighteen patients (67%) achieved seizure freedom over a median period of 10 months (range, 2-48 months). Eight of those patients (44%) were seizure free within 12 weeks of immunotherapy initiation. Eight patients (44%) had no residual deficits, but others experienced residual neurologic deficits, despite achieving seizure freedom. Cognitive and memory concerns were improved but persisted in 8 (44%). Four patients had behavioral or mood changes. One patient (patient 32) had residual aphasia having presented with intractable aphasic seizures and left cortical inflammatory changes. For long-term main-
tenance, immunotherapy comprised azathioprine only, 2; mycophenolate mofetil only, 11; or combinations of azathioprine, mycophenolate mofetil, prednisolone, rituximab, or methotrexate, 5.

Postimmunotherapy imaging was available for review in 15 of the patients whose scans had revealed evidence of inflammation (eTable 2). Four patients had no evidence of radiological changes. Five showed reduction in hyperintensity size, and 5 patients developed hippocampal atrophy and sclerosis. One patient with initial T2 hyperintensity in the right amygdalohippocampal region 3 months following seizure onset (E), which evolved to include the contralateral region 2 months later (F). Repeated MRI 3 months later before immunotherapy initiation demonstrated radiographic evidence of bilateral mesial temporal sclerosis (G) and residual left amygdala swelling and hyperintensity (H). Patient 3 presented with partial and secondary generalized seizures. There was signal abnormality in the right lateral temporal lobe (I) (arrow) after her first generalized tonic-clonic seizure, which occurred several weeks after the onset of partial seizures. Patient 11 was diagnosed with epilepsy paratonic continua and had abnormal signal in the left precentral gyrus (arrow) 2 months after seizure onset (J). Patient 7 developed status epilepticus after a 3-month history of complex partial seizures. Admission MRI revealed right thalamic and medial temporal hyperintensities (K). Patient 32 presented with generalized tonic-clonic seizure and subsequently developed antiepileptic drug–intractable aphasic seizures. Presentation MRI demonstrated pronounced signal abnormality in the left frontoparietal region (L).

One patient (patient 30) who had VGKC complex antibodies was seizure free for a 2-week period after receiving a third AED. An immunotherapy trial was initiated because of significant residual memory impairment but not for seizures; cognition improved within 3 months, and seizures did not recur. Four patients did not receive immunotherapy. Two patients declined, and the need for immunotherapy in the third patient (patient 2) was obviated because he became seizure free following removal of a thyroid papillary carcinoma found in the malignancy screening that was prompted by VGKC complex antibody detection. Seizure resolution followed. A fourth patient (patient 6), whose seizures also were associated with VGKC complex antibodies (3.5 nmol/L; normal range, ≤0.02 nmol/L), was refractory to the first AED (levetiracetam), but seizures were controlled after a second AED was started (lamotrigine). The AED therapy was discontinued after 3 years, and the patient remained seizure free 12 months later.
All 32 patients for whom we describe clinical, serologic, and imaging findings had refractory epilepsy of presumed autoimmune basis. The intractability, high seizure frequency, and striking improvement in seizure control achieved following immunotherapy in many warrant emphasis: 81% had significant improvement in seizure status and 67% achieved seizure freedom, a majority of whom were AED resistant.

Our study supports previously noted links between neurologic autoimmunity and epilepsy. Recurrent seizures were the early and predominant clinical manifestation in the patients of our report. An autoimmune etiology is identified most readily in patients who present with the full syndrome of limbic encephalitis, characterized by subacute memory impairment with affective changes and temporal lobe seizures. The diagnosis of autoimmune limbic encephalitis is aided by detection of neural autoantibodies with radiological or pathological evidence of temporal medial inflammation and in some cases a history of neoplasia in the preceding 5 years. Limbic encephalitis has been suggested as a precedent of hippocampal sclerosis and adult-onset temporal lobe epilepsy. In our report, one-third of the patients had seizures as their exclusive presentation without other recognized clinical accompaniments of limbic encephalitis. Although the remaining two-thirds had additional neurologic problems, including cognitive and personality changes, they had presented with predominant concerns of high daily seizure burden. This prevented clear distinction of the contribution of inflammatory limbic lesions vs seizure activity to the evolving neurocognitive impairment. Furthermore, 15 patients had normal MRI brain scans at initial presentation, and among 12 patients who had subsequent MRIs, a median of 4 months elapsed before subsequent imaging showed development of inflammatory changes in 5.

The primary aim of this study was to report the clinical features and immunotherapy response in a cohort diagnosed with autoimmune epilepsy. The study was not designed to compare clinical features of this entity with those of epilepsy from other etiologies. The diagnosis of autoimmune epilepsy requires a high level of suspicion at initial evaluation. The clinical presentations in our patients were heterogeneous, but some general observations can be made. Data from the current cohort suggest that autoimmune investigation should be considered in the presence of 1 or more of the following: an unusually high seizure frequency, intradividual seizure variability or multifocality, AED resistance, personal or family history of autoimmunity (either organ specific [e.g., thyroid disease, diabetes mellitus, pernicious anemia, or celiac disease] or non–organ specific [rheumatoid arthritis or systemic lupus erythematosus]), or recent or past neoplasia. Serological testing is increasingly valuable as an aid to establishing the diagnosis of an autoimmune etiology. As illustrated in the patients we presented, other laboratory and radiological findings may be normal. Serial MRI findings were consistent with inflammation in several patients. When detected, these radiological findings were consistent with inflammation in 5.

### Table 3. Epilepsy Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No./Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy for epilepsy (n = 27)</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up, mo, median (range)</td>
<td>17 (3-72) [10-31]</td>
</tr>
<tr>
<td>[IQR]</td>
<td></td>
</tr>
<tr>
<td>Seizure freedom</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Duration of seizure freedom, mo, median (range) [IQR]</td>
<td>10 (2-48) [4-17]</td>
</tr>
<tr>
<td>Seizure freedom =3 mo after immunotherapy</td>
<td>8/18 (44)</td>
</tr>
<tr>
<td>Seizure freedom &gt;3 mo after immunotherapy</td>
<td>10/18 (56)</td>
</tr>
<tr>
<td>Seizure improvement</td>
<td>4 (15)</td>
</tr>
<tr>
<td>No change</td>
<td>5 (18)</td>
</tr>
<tr>
<td>No immunotherapy for epilepsy (n = 5)</td>
<td></td>
</tr>
<tr>
<td>Resolved after cancer detected and treated</td>
<td>1</td>
</tr>
<tr>
<td>Resolved during AED treatment</td>
<td>2</td>
</tr>
<tr>
<td>Recommended but declined</td>
<td>2</td>
</tr>
</tbody>
</table>

**Abbreviations:** AED, antiepileptic drug; IQR, interquartile range.

*a* Patient who presented with daily seizures managed to achieve seizure freedom of approximately 2 weeks after trial of third AED. At this point, immunotherapy was instituted because of residual cognitive difficulties in the setting of voltage-gated potassium channel complex autoantibody.

- **Comment:** A majority of the patients in this study had neuronal VGKC complex autoantibodies. This serological marker aids the diagnosis of idiopathic and less commonly paraneoplastic autoimmune neurologic disorders. It is impressive that the seizure disorder was immunotherapy responsive in all seropositive patients. Voltage–gated potassium channel complex autoimmunity was first reported in patients with neumonotonia (Isaacs syndrome), Morvan syndrome, and limbic encephalitis. A broader spectrum of neurologic phenotypes affecting all levels of the nervous system has been described. Two independent groups recently reported that the target autoantigens in these disorders are generally not VGKC complex channel proteins per se but neuronal proteins (Lg1 and Caspr2) that respectively associate with a subset of Kv1 VGKC complexes at synapses and at juxtaparanodes of myelinated axons. Lg1 was the target antigen in 78% of our VGKC complex antibody–positive patients. One had antibodies targeting Caspr2. Previous reports have implicated Lg1 as the principal target antigen in limbic encephalitis, while Caspr2 is more commonly, but not exclusively, associated with peripheral nervous system manifestations. Lg1 is recognized as a causative gene in autosomal-dominant partial epi-
lepsy with auditory features. It encodes a secreted protein that links 2 epilepsy-related receptors, ADAM22 and ADAM23, creating a complex that incorporates presynaptic potassium channels and postsynaptic AMPA receptor scaffolds. Fukata and colleagues demonstrated that disruption of the Lgi1-linked synaptic complex causes abnormal synaptic transmission and epilepsy. Recently, faciobrachial dystonic seizures were reported to preceed Lgi1 antibody–associated encephalitis, suggesting that early immunotherapy could prevent the evolution to limbic encephalitis. We identified similar seizures in 6 of 14 (43%) Lgi1-seropositive patients in this cohort, often accompanied by other seizure semiologies. We also noted piloerection as a semiological feature in 4 of 14 (29%).

One patient in our study had NMDA receptor autoantibodies. N-methyl-D-aspartate receptor autoimmune encephalitis is often accompanied by ovarian teratoma and a stereotypic clinical evolution starting with a viral-like prodrome, psychiatric symptoms, memory impairment, dyskinesias, seizures, and progressing coma and hypoventilation. Most reported cases have had seizures at presentation, but these were overshadowed or accompanied by neurocognitive disturbances. Our patient presented with AED-intractable aphasic seizures and evolving left cortical inflammatory changes.

When autoimmune epilepsy is suspected on clinical grounds, CSF evaluation and comprehensive screening for neural autoantibodies are indicated. Selective autoantibody testing is not advised because no single neural antibody is definitively associated with seizures. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. If autoimmune epilepsy is suspected, a trial of 6 to 12 weeks of immunotherapy (IVMP or IVIg daily for 3 days and then weekly) is justifiable in the absence of other treatment options and may serve as additional evidence for an autoimmune etiology when a favorable seizure response is observed. In 22 of 27 patients (81%), this therapeutic trial was positive, and early treatment was associated with a favorable outcome (P < .05). Long-term immunosuppressive treatment, overlapping with gradual taper of IVMP or IVIg, should be considered for patients whose seizures respond favorably to the initial trial of immunotherapy. Despite this, relapses may still occur.

Our study is limited by its retrospective design and the fact that AED changes were not restricted during the period of immunotherapy. The patients’ poorly controlled seizures necessitated continuing AED changes during immunotherapy initiation, complicating interpretation of the contribution of immunotherapy to seizure control. However, the likelihood that such changes accounted for improved clinical response in these patients is well below the proportion of patients responding to immunotherapy trial. Clinical experience suggests that immunotherapy should not be used alone to control seizures but should be used in combination with AEDs to optimize seizure control. The clinical spectrum of autoimmune epilepsy is still unknown. In a series of patients with epilepsy, VGKC complex antibodies were detected in 10%; NMDA receptor antibodies, in 7% of newly diagnosed patients; and GAD65 antibodies, in 1.6% to 1.7%. It is conceivable that we are only identifying patients with the most severe presentations in this heterogeneous group, and the burden of this entity remains underappreciated in patients with milder epilepsies. Questions remaining unanswered include the natural history of autoimmune epilepsy, the selection criteria for patients with epilepsy most likely to benefit from an autoimmune evaluation, the timing for immunotherapy trial, and optimal duration of long-term immunotherapy maintenance.

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Online-Only Material: The eTables and eFigure are available at http://www.archneurol.com. Visit http://www
..archneurol.com to listen to an author interview about this article.

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