Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy

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ABSTRACT

Objective: To evaluate a trial of immunotherapy as an aid to diagnosis in suspected autoimmune epilepsy.

Method: We reviewed the charts of 110 patients seen at our autoimmune neurology clinic with seizures as a chief complaint. Twenty-nine patients met the following inclusion criteria: (1) autoimmune epilepsy suspected based on the presence of $\geq$1 neural autoantibody (n = 23), personal or family history or physical stigmata of autoimmunity, and frequent or medically intractable seizures; and (2) initiated a 6- to 12-week trial of IV methylprednisolone (IVMP), IV immune globulin (IVIg), or both. Patients were defined as responders if there was a 50% or greater reduction in seizure frequency.

Results: Eighteen patients (62%) responded, of whom 10 (34%) became seizure-free; 52% improved with the first agent. Of those receiving a second agent after not responding to the first, 43% improved. A favorable response correlated with shorter interval between symptom onset and treatment initiation (median 9.5 vs 22 months; p = 0.048). Responders included 14/16 (87.5%) patients with antibodies to plasma membrane antigens, 2/6 (33%) patients seropositive for glutamic acid decarboxylase 65 antibodies, and 2/6 (33%) patients without detectable antibodies. Of 13 responders followed for more than 6 months after initiating long-term oral immunosuppression, response was sustained in 11 (85%).

Conclusions: These retrospective findings justify consideration of a trial of immunotherapy in patients with suspected autoimmune epilepsy.

Classification of evidence: This study provides Class IV evidence that in patients with suspected autoimmune epilepsy, IVMP, IVIg, or both improve seizure control. *Neurology*® 2014;82:1578–1586

GLOSSARY

AED = antiepileptic drug; **CASPR2** = contactin-associated protein-like 2; **CC** = calcium channel; **gAChR** = neuronal acetylcholine receptor, ganglionic-type; **GAD65** = glutamic acid decarboxylase 65; **IgG** = immunoglobulin G; **IVIg** = IV immune globulin; **IVMP** = IV methylprednisolone; **LGI1** = leucine-rich, glioma-inactivated 1; **PMA Abs** = antibodies to neural plasma membrane antigen; **VGKC** = voltage-gated potassium channel.

Approximately one-third of epilepsy cases are intractable to antiepileptic drug (AED) therapy.[1] Seizures are recognized as a common manifestation of autoimmune limbic encephalitis and multifocal paraneoplastic disorders.[2–9] Accumulating evidence supports an autoimmune basis for seizures in the absence of syndromic manifestations of limbic encephalitis for a subset of AED-resistant epilepsy.[10–15] Expedited diagnosis is imperative because early initiation of immunotherapy facilitates improvement.[10]

When syndromic features of limbic encephalitis are lacking, the diagnosis of autoimmune epilepsy is often delayed. Valuable aids to the diagnosis include neural autoantibody detection, radiologic evidence of temporomesial inflammation, and CSF evidence of neuroinflammation.[3,10] Valuable clinical clues are subacute onset, an unusually high seizure frequency, intraindividual seizure variability or multifocality, AED resistance, personal or family history of autoimmunity, or history of recent or past neoplasia (figure 1).[10]

Supplemental data
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- Acute to subacute onset (maximal seizure frequency ≤ 3 months)
- Multiple seizure types or faciobrachial dystonic seizures
- AED resistance
- Personal or family history (1st degree relative) of autoimmunity
- History of recent or past neoplasia
- Viral prodrome
- Evidence of CNS inflammation
  - CSF (elevated protein, pleocytosis, oligoclonal bands, + CSF index)
  - MRI (mesial temporal or parenchymal T2 hyperintensity)
  - Hypermetabolism on functional imaging (PET)
- Detection of neural autoantibody

AED = antiepileptic drug.

IV methylprednisolone (IVMP), IV immune globulin (IVIg), and plasma exchange are accepted and safe therapies for patients with suspected autoimmune neurologic disorders.[16–19] Their use as part of a diagnostic algorithm has been advocated but not formally evaluated.[20–22] Response to an immunotherapy trial can support the diagnosis of autoimmune epilepsy[21,22] and can help identify those most likely to respond to maintenance immunosuppressive therapy.

There are no current guidelines for choice of agent, length of treatment, or indications for switching to a second agent. As a result, practice varies widely between individual practitioners. This study evaluates the utility of an immunotherapy trial protocol developed at our institution for the evaluation and management of patients with suspected autoimmune epilepsy.

METHODS **Standard protocol approvals, registrations, and patient consents.** The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB 08-006647).

Patients. Using a text word search for "epilepsy" or "seizures," the Mayo Clinic Records Linkage system was used to identify patients seen in the Autoimmune Clinic between January 1, 2011, and September 31, 2012, with possible autoimmune epilepsy (figure 2). We also reviewed the charts of patients who were the subject of a previous report.[10] We included patients who fulfilled the following criteria: (1) intractable seizures as the exclusive (n = 12) or predominant (n = 17) presenting complaint; (2) an autoimmune etiology suspected on the basis of clinical presentation (figure 1), inflammatory CSF, MRI characteristics suggesting inflammation, or detection of a neural autoantibody; (3) initiated a 6- to 12-week therapeutic trial of IVMP, IVIg, or both. Patients who were also initiated on long-term oral immunosuppressants at the onset of the trial were excluded. The choice of agent was determined by clinician preference.

Demographic, clinical (seizure semiology, course, associated symptoms), and radiologic characteristics and autoimmune serology were reviewed.

EEG studies were performed in all subjects before the immunotherapy trial and were repeated in most subjects after the trial was completed. The international 10–20 system for electrode placement was used for acquisition of all EEG recordings. Routine EEGs comprised 21-channel recordings and extended EEG monitoring studies comprised 30-channel digital recordings.

Seizure frequency at presentation was obtained via review of the medical record. Baseline seizure frequency was determined by reviewing the seizure frequency stated to be present in the patients' initial consultations prior to initiation of treatment, and subsequently categorized as daily (≥1 seizure per day), weekly (≥1 seizure per week but not daily), or monthly (≥1 seizure per month but not weekly). As this was a retrospective study, the way in which the seizure rates were documented in the record varied from patient to patient, and it was not always made clear as to the period of time over which the seizure frequency stated at the time of initial consultation had been occurring in all cases (e.g., some charts indicated a daily rate, others a weekly, and others a monthly rate; some charts did not indicate over what period of time a given frequency had been occurring). Thus, documented seizure frequencies were converted to a weekly rate to enable calculation of baseline posttreatment frequency. Response to the immunotherapy trial was determined by review of the record for seizure quantification during the periods of time following initiation of treatment in a similar manner. To facilitate statistical analysis of immunotherapy trial effect using statistical methods for categorical data, the results of immunotherapy were subsequently categorized as showing "seizure freedom," "improvement" (denoting those with a reduction in seizure frequency by more than 50%), or "no change." The time to response was based on patient report at the conclusion of the trial during follow-up appointments.

We also assessed whether response was sustained in a subset of patients for whom we had follow-up data spanning greater than 6 months. This was based on patient report at the time of the last visit.

Data were expressed as median, range, and SD for continuous variables and counts (percentages) for categorical variables. Differences between responders and nonresponders were compared using an unpaired t test for continuous measures and Fisher exact tests for categorical variables.

Classification of evidence. This study provides Class IV evidence that in patients with suspected autoimmune epilepsy, IVMP, IVIg, or both improve seizure control.

RESULTS **Clinical characteristics.** Table e-1 on the *Neurology*® Web site at Neurology.org shows clinical, radiologic, EEG, autoimmune, serologic, and CSF findings for all patients. Seizures were present for a median duration of 12 months (range 1–120 months). Fifty-five percent were female; median age at seizure onset was 53 years (range 2–79 years). The evidence of an inflammatory etiology included detection of 1 or more neural autoantibodies in serum (79%) and compatible abnormalities in CSF (69%) or MRI (62%).

At presentation, 86% of patients had ictal or interictal epileptiform abnormalities on EEG. Ten out of 29 (34%) had focal seizures without impaired awareness, including 1 with epilepsia partialis continua, 23/29 (79%) had focal seizures with impaired awareness, and 9/29 (31%) had secondary bilateral convulsive seizures. Seizures at presentation occurred daily

Figure 2   **Patient selection**
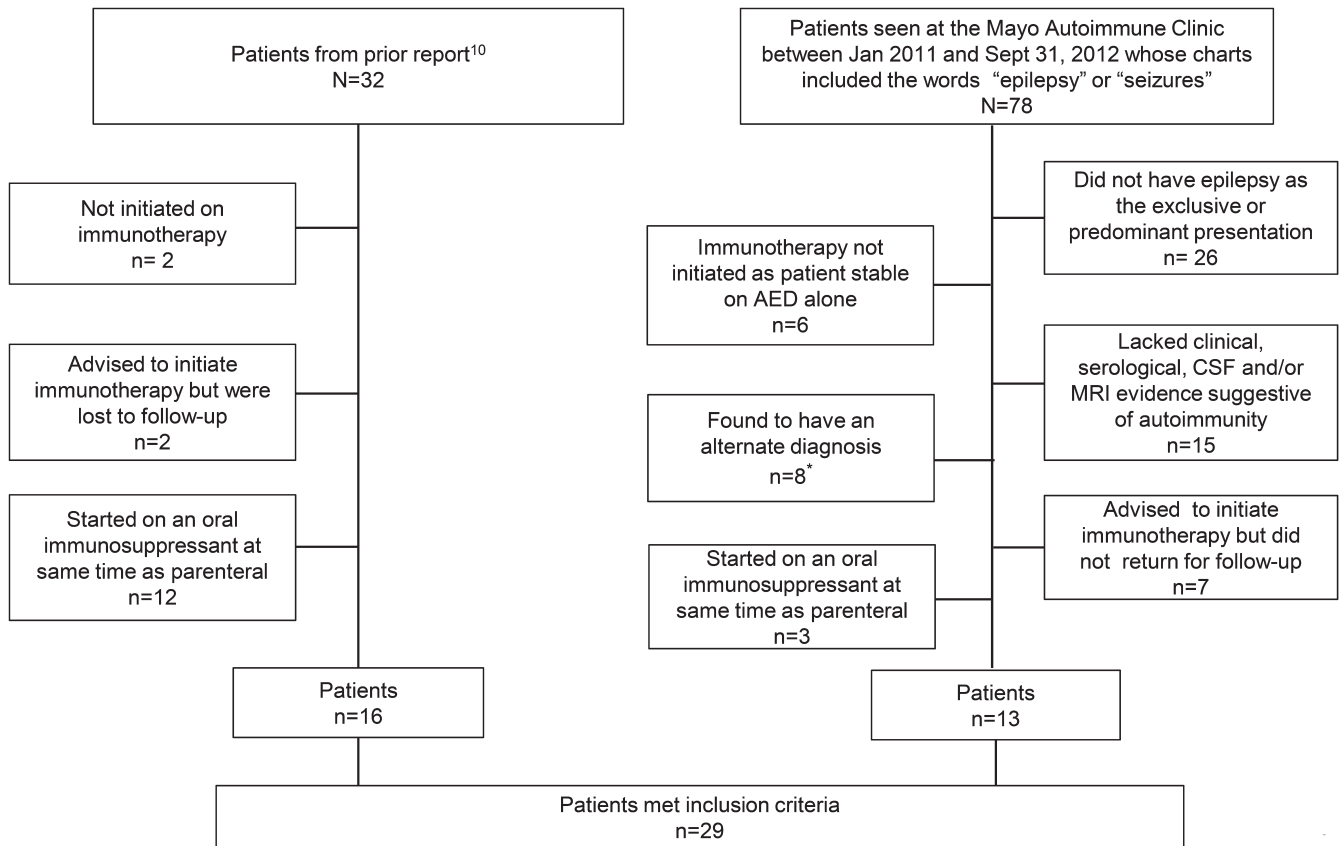
*Multiple sclerosis 1, possible cerebroretinal microangiopathy with calcifications and cysts 1, gliomatosis cerebri 2, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) 1, nonepileptic behavioral spells 2, alcohol withdrawal seizures 1. AED = antiepileptic drug.

in 69% of patients and 59% had received 2 or more AEDs (median 3). Four of 12 patients (33%) who were seropositive for voltage-gated potassium channel (VGKC) complex immunoglobulin G (IgG) had facio-brachial dystonic seizures: 2 per history and 2 recorded at our institution on video-EEG.

Autoantibody profiles. Neural autoantibodies were identified (table 1, figure 3) in 23 patients (79%). Sixteen patients had antibodies to neural plasma membrane antigens (PMA Abs): VGKC complex, 12 (leucine-rich, glioma-inactivated 1 [LGI1]–specific, 11; contactin-associated protein-like 2 [CASPR2]–specific, 1); neuronal acetylcholine receptor, ganglionic-type (gAChR), 3; voltage-gated calcium channel and P/Q-type and N-type (CC P/Q, CC N), 1. Six patients had antibodies to glutamic acid decarboxylase 65 (GAD65), only one of whom had comorbid diabetes mellitus type 1. One patient had onconeural antibodies (Ma1 and Ma2).

Response to immunotherapy trial. All patients received a protocol currently standardized in the Mayo Autoimmune Neurology Clinic: daily infusions of 1,000 mg of IVMP or 0.4 g/kg IVIg for 3–5 days, followed by weekly infusions for 6–12 weeks at the same dose.

A total of 18 patients (62%) responded favorably to the immunotherapy trial (table 1, figure 3). Ten of these (56%) achieved seizure freedom and the remainder had more than 50% reduction in seizure frequency. Five of 11 responders with daily seizures (45%) became seizure-free after completion of the immunotherapy trial, 45% had only monthly seizures, and 1/11 (9%) had weekly seizures (table e-1). This last patient had reported upwards of 50 focal seizures without dyscognitive features a day prior to the trial but only 2 or 3 a week after its completion. Two out of 4 responders with weekly seizures (50%) became seizure-free and the other 2 had monthly seizures. All 3 responders with monthly seizures became seizure-free. None of the responders who had generalized tonic-clonic seizures at presentation (8/18; 44%) continued having these after completion of the trial (table e-1).

Fifteen patients (52%) responded to the first agent tried and 14 (48%) did not. Having failed the first agent, 3 of 7 patients (43%) responded to a second agent (figure 3).

Of the 15 patients who improved with the first immunotherapy trial, 6 responded within the first week, 6 responded in the second to fourth weeks,

Table 1 Summary of clinical characteristics of responders and nonresponders

Characteristics	Responders (n = 18)	Nonresponders (n = 11)	p Value
Sex			
Female	9 (50)	7 (64)	0.702
Seizure characteristic			
Age at onset, y, median (range) [SD]	53.5 (2-74) [18.04]	53 (12-79) [18.57]	0.683
Duration of seizures, mo, median (range) [SD]	9.5 (1-96) [23.18]	22 (4-120) [36.19]	0.048
Seizure type			
Focal seizures without impaired awareness	8 (44)	2 (18)	0.234
Focal seizures with impaired awareness	14 (78)	9 (82)	1.00
Generalized tonic-clonic	8 (44)	1 (9)	0.096
Faciobrachial dystonic seizures	4 (22)		0.268
Multiple seizure types	10 (55.5)	1 (9)	0.019
No. of AEDs at time of trial			
≤1	7 (38.8)	5 (45.5)	1.00
≥2	11 (61)	6 (54.5)	1.00
Changes in antiepileptic Tx during trial	5 (27.7)	1 (9)	0.362
Seizure frequency at time of diagnostic trial			
≥1/d	11 (61)	9 (82)	0.412
≥1/wk	4 (22)	2 (18)	1.00
≥1/mo	3 (17)		0.269
Subacute presentation	16 (88.8)	6 (54.5)	0.071
Coexisting autoimmune disease	9 (50)	6 (54.5)	1.00
Family history of autoimmune disease	5 (27.7)	2 (18)	0.677
Past history of neoplasm	1 (6)	2 (18)	0.539
Viral prodrome	1 (6)	2 (18)	0.539
MRI with probable inflammatory changes	12 (67)	6 (54.5)	0.697
CSF changes	13 (72)	7 (64)	0.694
Elevated protein (>35 mg/dL)	11 (61)	6 (54.5)	1.00
Elevated leukocyte count	2 (11)	0	0.512
Oligoclonal bands or elevated IgG	1 (6)	3 (27.2)	0.138
Index/synthesis rate			
Neuronal autoantibody status			
No neuronal Abs	2 (11)	4 (36)	0.163
Neuronal autoantibody	16 (89)	7 (64)	0.163
Abs to plasma membrane Ags	14 (78)	2 (18)	0.002
Gad 65 Abs	2 (11)	4 (36)	0.163
Onconeural Abs (Ma1/Ma2)	0	1 (9)	0.379

Abbreviations: Abs = antibodies; AED = antiepileptic drug; Gad65 = glutamic acid decarboxylase 65; IgG = immunoglobulin G. Data are n (%), unless otherwise indicated.

and 1 required treatment for 5 weeks before improvement was noted. Time to response was not available for 2 patients (17%). For the 3 patients who reported improvement with the second immunotherapy trial, 1 responded within the first week and 2 responded between the second and fourth weeks (table e-1).

Three patients categorized as responders (17%) underwent a change in AEDs during the trial, and another 1 (6%) had a dose increment (table e-1, table 1). The ketogenic diet was initiated for 1 responder after a favorable response to IVIg.

Two responders received plasmapheresis towards the end of IVMP trial due to relapse in spite of initial response; both had favorable outcomes (table e-1).

Responders vs nonresponders. The interval from seizure onset to initiation of the immunotherapy protocol
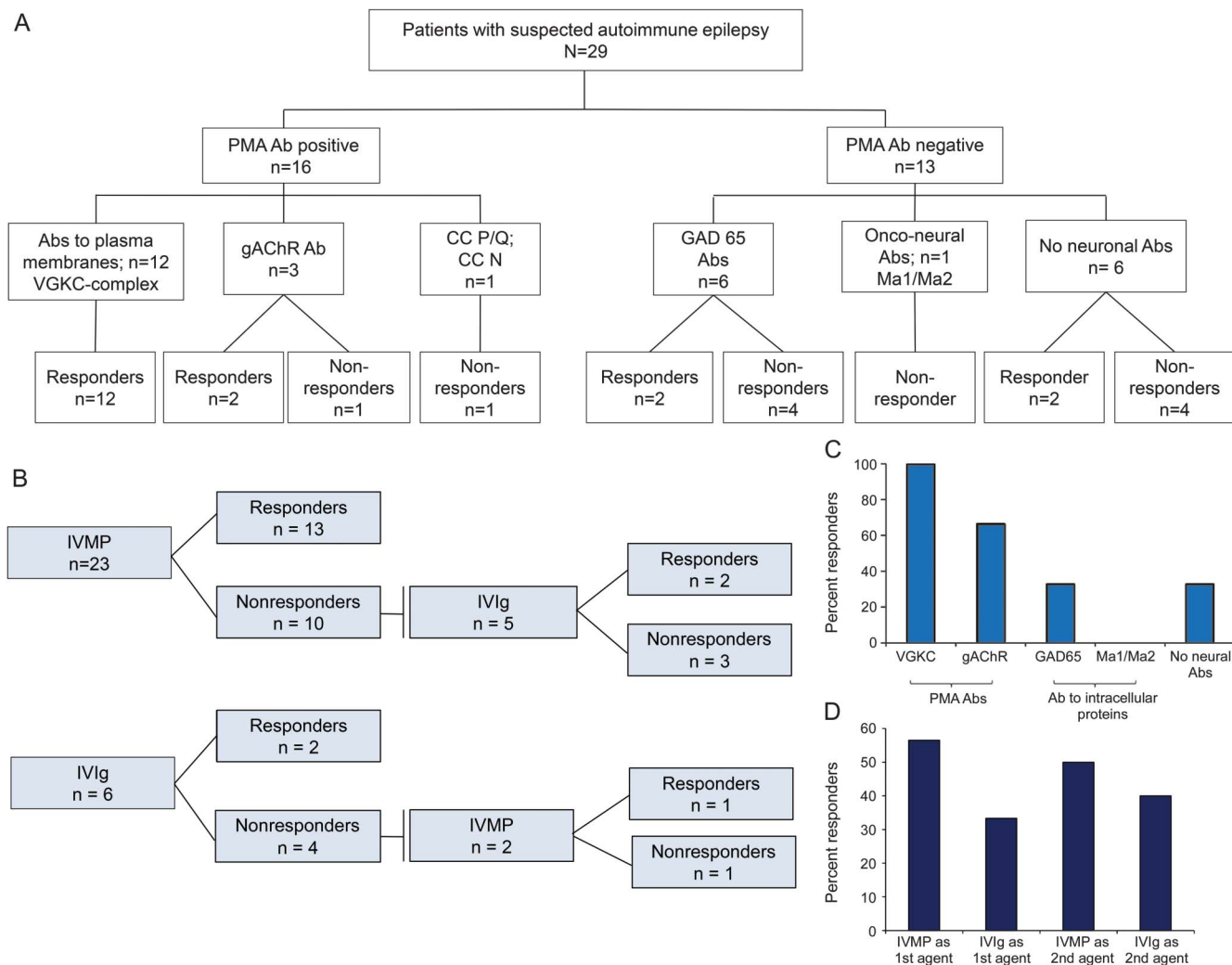
(A) Flow chart of response to immunotherapy trial according to antibody type. (B) Flow chart of response to immunotherapy trial according to immunotherapeutic agent tried. (C) Percent of responders by antibody type. (D) Percent of responders to first and second immunotherapeutic agent tried. Abs = antibodies; CC N and CC P/Q = voltage-gated calcium channel N-type and P/Q-type; gAChR = neuronal ganglionic nicotinic acetylcholine receptor antibody; GAD65 = glutamic acid decarboxylase 65; IVIg = IV immune globulin; IVMP = IV methylprednisolone; PMA Ab = plasma membrane antigen antibodies; VGKC = voltage-gated potassium channel.

was shorter for responders compared with nonresponders (median 9.5 vs 22 months, $p = 0.048$) (table 1). Although not statistically significant, neural autoantibodies were more frequent in responders compared with nonresponders (89% vs 64%). Responders were more likely than nonresponders to have PMA Abs (78% vs 18%, $p = 0.002$) (table 1).

No seizure class predicted outcome but responders were more likely to have multiple seizure types than nonresponders (55.5% vs 9%, $p = 0.019$) (table 1). The majority of responders had subacute onset (88.8%), compared to 54.5% of nonresponders, although the difference was not statistically significant ($p = 0.071$) (table 1).

Fourteen of 16 (87.5%) patients with PMA Abs responded. In patients with antibodies directed at intracellular components, 2 of 6 GAD65 antibody–
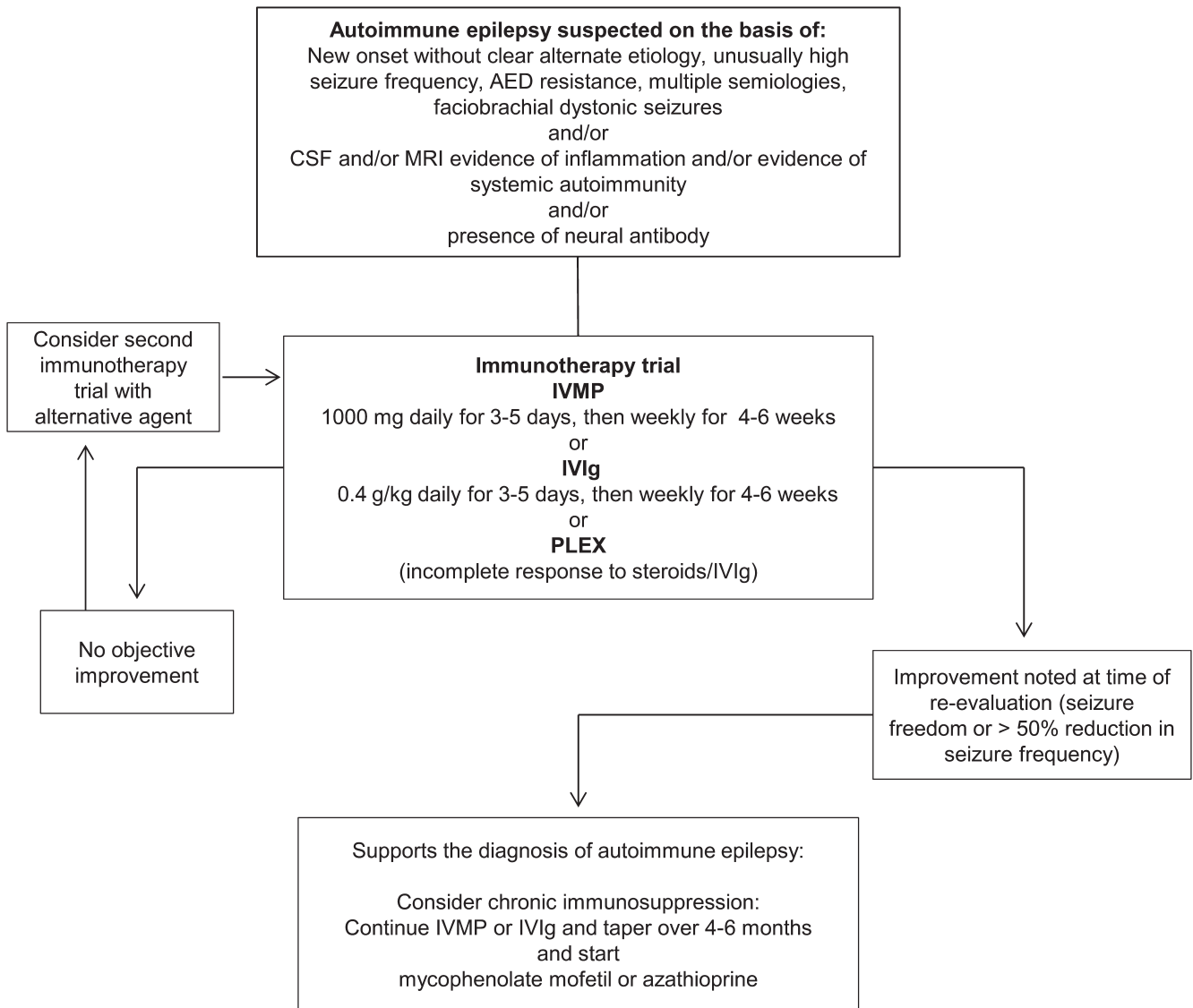
positive patients (33%) responded favorably, whereas the sole patient with an onconeural antibody did not respond. Two of 6 patients (33%) with no neural antibody detected responded (table 1, figure 3).

After completion of the trial, EEG became essentially normal in 10/14 (71%) responders who had epileptiform discharges at presentation, compared to 1/11 (9%) in nonresponders. MRI showed improvement in 8/12 (67%) responders. MRI remained unchanged in the 6 nonresponders with abnormalities (table e-1).

Adverse events. Six subjects (21%) reported side effects (table e-1). Adverse events prompted cessation of trial in 2 cases (7%): 1 with steroid-induced psychosis and another with IVIg-associated aseptic meningitis.

Subsequent maintenance immunosuppression. Sixteen responders (89%) commenced long-term

Autoimmune epilepsy suspected on the basis of:
New onset without clear alternate etiology, unusually high seizure frequency, AED resistance, multiple semiologies, faciobrachial dystonic seizures
and/or
CSF and/or MRI evidence of inflammation and/or evidence of systemic autoimmunity
and/or
presence of neural antibody

Consider second immunotherapy trial with alternative agent

Immunotherapy trial
IVMP
1000 mg daily for 3-5 days, then weekly for 4-6 weeks
or
IVIg
0.4 g/kg daily for 3-5 days, then weekly for 4-6 weeks
or
PLEX
(incomplete response to steroids/IVIg)

No objective improvement

Improvement noted at time of re-evaluation (seizure freedom or > 50% reduction in seizure frequency)

Supports the diagnosis of autoimmune epilepsy:

Consider chronic immunosuppression:
Continue IVMP or IVIg and taper over 4-6 months
and start
mycophenolate mofetil or azathioprine

AED = antiepileptic drug; IVIg = IV immune globulin; IVMP = IV methylprednisolone; PLEX = plasma exchange.

oral immunosuppressant therapy: mycophenolate mofetil in 14 and azathioprine in 2 (table e-1). Thirteen of these patients were followed for longer than 6 months, and the beneficial response was sustained in 11 (85%). At least 1 anticonvulsant medication was continued in all 13 cases. The 2 patients who relapsed were GAD65-IgG seropositive.

Of the 2 responders who did not commence long-term immunosuppressant therapy, one is receiving carbamazepine monotherapy and remains seizure-free, and the other (maintained on the ketogenic diet and no anticonvulsant therapy) relapsed and was to commence IVIg therapy at the time of last follow-up.

Two nonresponders (18%) were started on oral long-term immunosuppression and one responded. Three additional nonresponders (27%) experienced seizure improvement with addition of carbamazepine or lacosamide.

DISCUSSION The most important question posed by a patient with medically intractable epilepsy and a suspected autoimmune basis is whether the seizures will be immunotherapy responsive. A positive response to an immunotherapy trial, as described in this study, supports an immune-mediated etiology and justifies consideration of long-term maintenance immunotherapy. We observed striking improvement in seizure control with a relatively low side-effect profile, despite high seizure frequency and medical intractability at presentation. Fewer than a quarter of subjects experienced side effects, and only in 2 cases were these severe enough to prompt cessation of the immunotherapy trial.

The delay from onset of seizures to initiation of the immunotherapy trial was significantly longer for nonresponders than for responders, including some nonresponders who were seropositive for neural autoantibodies. This supports prior evidence

suggesting that early treatment favors a beneficial response.[10] Eighty-three percent of responders reported benefit with the first agent tried (either IVMP or IVIg). Close to half of initial nonresponders improved after consenting to a trial with the second agent. These findings justify a trial of an alternative immunosuppressant when the suspicion for autoimmune epilepsy remains high. The majority of patients (79%) were initiated on IVMP. IVIg tended to be the first agent used in pediatric patients or in those with GAD65 antibodies. This likely reflects its perceived favorable side effect profile in the case of children and the concern that treatment with IVMP may lead to the development of diabetes mellitus in those with GAD65 seropositivity. Currently, there is not enough evidence to recommend one over the other.

More than 83% of responders reported benefit within 4 weeks of initiating therapy. We therefore anticipate that a shorter immunotherapy trial (4–6 weeks) than our current protocol may suffice. We make this recommendation for the length of the "immunotherapy trial" protocol and the appropriate time of crossover as guidance for clinicians confronting the challenge of diagnosing and managing the therapy of such patients (figure 4).

Although no single seizure class was predictive of response, patients with multiple seizure types were more likely to respond. Subacute onset at presentation was associated with a positive response to the immunotherapy trial but this was not statistically significant. Only one-third of VGKC complex IgG-positive patients had faciobrachial dystonic seizures.

The majority of responders (78%) had antibodies to plasma membrane antigens. Most (85%) had VGKC complex autoantibodies but 2 had gAChR antibodies. Although all the patients with VGKC complex IgG antibodies included in this study responded, immunotherapy-resistant cases have been reported. It has become clear that VGKC antibodies are not directed against the VGKC itself, but target other proteins within the VGKC complex. Antigenic targets include LGI1 and CASPR2, both of which have extracellular plasma membrane components.[5,6] However, in a proportion of patients with VGKC antibodies, a specific antigenic target has not been identified and it is possible that a subset of these patients have antibodies directed at an intracellular portion of the complex. Response to an immunotherapy trial in patients with positive VGKC complex IgG antibodies helps confirm the pathogenic role of these antibodies in patients with suspected autoimmune epilepsy.

The high representation of GAD65 antibody–positive patients in the nonresponder group (two-thirds) likely reflects the cytoplasmic-facing location of the GAD65 synaptic vesicle antigen. IgGs specific for cytoplasmic and nuclear autoantigens are considered surrogate markers for inflammatory organ-specific disorders mediated by cytotoxic T cells specific for peptides derived from the intracellular proteins defined by those autoantibodies. These disorders generally respond less well to immunotherapy. Patients who responded despite having high serum levels of GAD65 antibody likely have coexisting autoantibodies targeting as yet unrecognized plasma membrane antigens, such as the glycine receptor autoantibody recently demonstrated to coexist with GAD65 antibody in some patients with stiff-man syndrome.[23,24] Similarly, one-third of patients with absent neural antibodies responded. These apparently seronegative patients may harbor as yet unidentified autoantibodies targeting plasma membrane antigens. Thus the absence of a neural antibody in the appropriate clinical context should not preclude consideration of an immunotherapy trial.

Although a positive response to immunotherapy supports an immune-mediated etiology, immunotherapy has been used in the treatment of intractable epilepsies not proven to be autoimmune, as is the case with infantile spasms or Landau-Kleffner syndrome and electrical status epilepticus of sleep.[25,26] Conversely, patients with neuronal antibodies who fail to respond to immunotherapy may still have an autoimmune basis for their seizures, as is likely the case in patients with onconeural antibodies targeting intracellular proteins. Our study confirms prior published data demonstrating that PMA Abs predict a positive response to immunotherapy[15,21] but beneficial outcomes were observed in both antibody-positive and antibody-negative patients. Different guidelines have been proposed to identify and classify CNS autoimmunity.[20,22,27] Although helpful, these guidelines fail to predict treatment response. In cases of suspected autoimmune epilepsy, response to an immunotherapy trial remains a powerful predictor of outcome.

This study is limited by small numbers, a retrospective design, and lack of systematic crossover (from IVMP to IVIg or vice versa). Patients were seen at a specialized autoimmune clinic, making the study subject to referral bias. In some cases, the decision to treat may have been guided by disease severity and an immunotherapy trial initiated even if the autoimmune nature of the epilepsy was not completely clear. Conversely, patients who may have responded to a second immunotherapy agent were not tried on one if symptoms were not severe enough. Also, likely confounders such as AED medication changes during the trial could not be controlled for and nonresponders may have been lost to follow-up. The seizure quantification methodology available to us was not ideal. The preferred seizure quantification would be to calculate a prospective baseline measurement over a defined period prior to initiation of immunotherapy, followed by weekly seizure

rates after intervention. Regrettably, the retrospective nature of this study prevented ascertaining seizure frequency in this manner. Given the sometimes dramatic results in many patients, however, the lack of precise measurement in this cohort was not likely to have affected the central observations in this study. A randomized controlled trial with a crossover design would help to further specify treatment effect and would limit confounders. Such a study may also help identify patients who benefit differentially from IVMP and IVIg and could better define the population of patients most likely to respond to the trial.

This retrospective study describes the clinical experience of a single center in using an immunotherapy trial in the evaluation of patients with suspected autoimmune epilepsy.

The findings provide persuasive evidence for a subset of patients with medically intractable epilepsy having an autoimmune-mediated basis for their epilepsy, and justify undertaking a trial of immunotherapy to support the diagnosis and guide future management.

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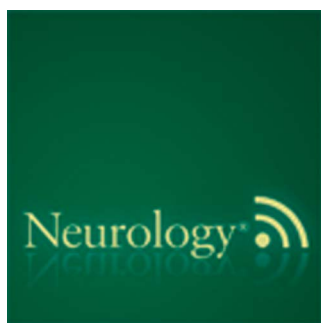
Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy (See p. 1578)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the May 6, 2014, issue of *Neurology*. In the second segment, Dr. John Mytinger talks with Dr. Sean Pittock about his paper on the utility of an immunotherapy trial in the evaluation of patients with presumed autoimmune epilepsy. Dr. James Addington reads our e-Pearl of the week about logopenic-variant primary progressive aphasia. In the next part of the podcast, Dr. Mike Brogan focuses his interview with Dr. Pratik Pandharipande on delirium in acute brain dysfunction in critically ill patients.

Disclosures can be found at www.neurology.org.

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