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Epilepsia®

GRAY MATTERS

Letter

# Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability

To the Editors:

In 2017, we validated models to predict seropositivity of neural-specific antibodies and favorable response to an immunotherapy trial among patients with epilepsy.[1] The purpose of these models is to optimize selection of cases for autoimmune epilepsy evaluation and management.

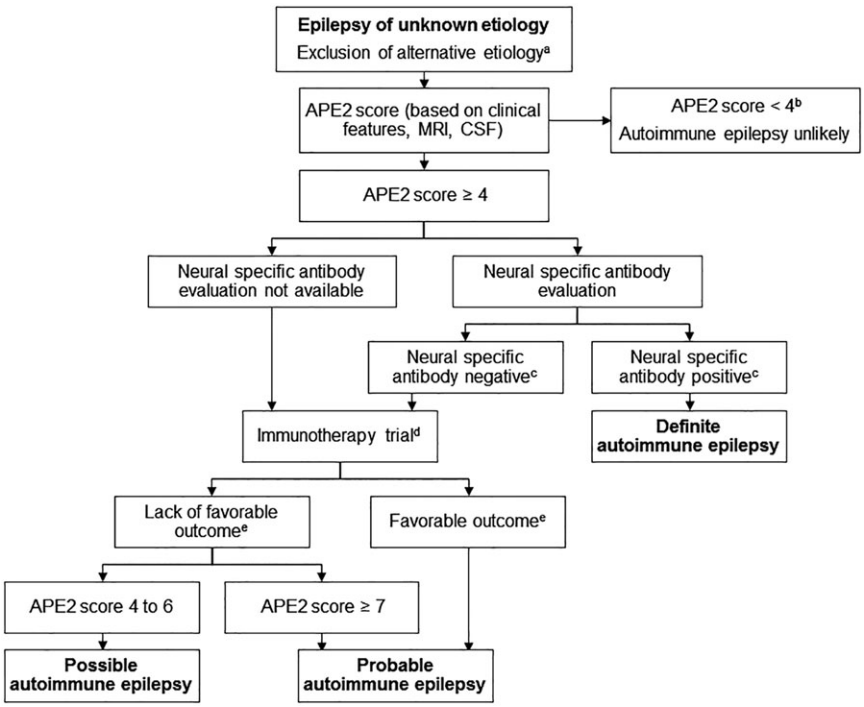


**FIGURE 1** Autoimmune epilepsy diagnostic criteria stratified as per Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score and neural antibody status. Algorithm is shown for utilization of proposed diagnostic criteria for autoimmune epilepsy diagnosis. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

[a]Reasonable exclusion of alternative etiology (genetic, infectious encephalitis, neoplasm, neurodegenerative process, or metabolic or toxic encephalopathy).

[b]One patient with leucine-rich glioma-inactivated protein-1 antibody had APE2 score < 4. He had monophasic clinical course with seizures responding to lacosamide and intravenous methylprednisolone.

[c]Neural-specific antibodies clinically validated to have an association with autoimmune epilepsy (AMPAR [amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor], amphiphysin, AK5 [adenylate kinase 5], ANNA1 [antineuronal nuclear antibody 1], ANNA2 [antineuronal nuclear antibody 2], ANNA3 [antineuronal nuclear antibody 3], DPPX [dipeptidyl-peptidase–like protein 6], CASPR2 [contactin associated protein 2], CRMP5 [collapsin response-mediator protein 5], GAD65 [glutamic acid decarboxylase 65, serum >20 $nmol \cdot L^{-1}$ or CSF-detected], GABABR [γ-aminobutyric acid B receptor], GABAAR [γ-aminobutyric acid A receptor], GFAPα [glial fibrillary acidic protein, CSF-detected], LGI1 [leucine-rich glioma-inactivated protein 1], Ma1/Ma2, MOG [myelin oligodendrocyte glycoprotein], mGluR5 [metabotropic glutamate receptor 5], neurexin-3α, NMDAR [*N*-methyl D-aspartate receptor, preferably CSF-detected], PCA2 [Purkinje cell antibody type 2], PCA Tr) evaluated and confirmed by the latest validated techniques.

[d]Standardized immunotherapy trials should be considered. Twelve-week intravenous methylprednisolone (IVMP) trial: 1 g, intravenously once per day for 3 consecutive days, then once weekly for 5 weeks, followed by once every 2 weeks for 6 weeks, for a total of 12 weeks of therapy. Six-week IVMP trial: 1 g, intravenously once per day for 3 consecutive days, then once weekly for 5 weeks. Twelve-week intravenous immunoglobulin (IVIG) trial: 0.4 g/kg daily for 3 days followed by 0.4 g/kg every week for 6 weeks and then every 2 weeks for 6 weeks. Six-week IVIG trial: 0.4 g/kg daily for 3 days followed by 0.4 g/kg every week for 6 weeks.

[e]Favorable outcome is defined as >50% reduction in seizure frequency

Recently, we expanded the scope of these models for management of autoimmune encephalopathy. We made a few modifications that improved the accuracy of these models (Table S1).[2] The purpose of this letter is to share the latest and more accurate version of these models, which are applicable to epilepsy.

Modifications: (1) Magnetic resonance imaging (MRI) brain criteria were expanded beyond the previously published unilateral/bilateral medial temporal lobe T2 or fluid-attenuated inversion recovery (FLAIR) hyperintensities. We now also include multifocal T2/FLAIR hyperintensities that are compatible with demyelination or inflammation involving gray matter, white matter, or both.[3] (2) We now score only cancers diagnosed within 5 years of seizure or encephalopathy onset.[4] (3) We increased the weighted score of faciobrachial-dystonic seizure,[5] a pathognomic feature of leucine-rich glioma-inactivated protein 1 antibodies. We utilized Rasch analysis, which supported the differential weighting of items based or higher or lower level of predictive potential. This analysis demonstrated lack of major item dependencies among the variables included in the scoring system.[2]

Increased specificity: The application of Antibody Prevalence in Epilepsy and Encephalopathy (APE2) scores to the patients with epilepsy of unknown etiology (n = 262) led to an increase in the receiver operating curve area from 0.94 to 0.97 (95% confidence interval = 0.95-0.99; Figure S1). Additionally, the specificity of APE2 score ≥ 4 among patients with epilepsy of unknown etiology increased from 79% to 85%, without a change in sensitivity (98%). Among the evaluated patients, APE2 score ≥ 7 demonstrated specificity of 100% for an autoimmune etiology (17 neural-specific antibody-positive patients, three neural-specific antibody-negative limbic encephalitis patients). The sensitivity (88%) and specificity (84%) of Response to Immunotherapy in Epilepsy and Encephalopathy score ≥ 7 computed only for patients receiving immunotherapy trial (n = 77) remained unchanged.

Diagnostic criteria: We suggest diagnostic criteria for autoimmune epilepsy based on APE2 score, neural-specific antibody serum status, and trial of immunotherapy[6] (Figure 1). All patients with epilepsy of unknown etiology and APE2 score ≥ 4 should undergo autoantibody evaluation. If the neural-specific antibodies clinically validated to be associated with autoimmune epilepsy are positive (Figure 1), these cases meet the criteria for "definite autoimmune epilepsy." A diagnostic trial of immunotherapy should be considered for patients with APE2 score ≥ 4, negative autoantibody evaluation, and no clear alternative etiology for epilepsy. A favorable response to immunotherapy trial[6] or APE2 score ≥ 7 (due to high specificity) supports the diagnosis of "probable autoimmune epilepsy," whereas patients with APE2 score = 4-6 who are refractory to immunotherapy trial remain in the "possible autoimmune epilepsy" category. Prior to undertaking this algorithmic approach, an initial workup including a thorough clinical evaluation, electroencephalography, brain MRI, and cerebrospinal fluid analysis is recommended. This will not only help with optimal scoring of APE2 variables but would also help rule out alternative etiologies. The proposed diagnostic algorithm may aid clinicians in the management of epilepsy of unknown etiology.

## AUTHOR CONTRIBUTIONS

Concept and design, acquisition of data, and analysis and interpretation of data: all authors. Drafting of manuscript: D.D. Critical revision: S.J.P. and A.M.

## DISCLOSURE OF CONFLICTS OF INTEREST

D.D. has no conflicts of interest to report. S.J.P. and Mayo Clinic have a financial interest in patents (#12/678,350 filed 2010 and #12/573,942 filed 2008) that relate to functional AQP4/NMO-IgG assays and NMO-IgG as a cancer marker. S.J.P. has provided consultation to Alexion Pharmaceuticals, Medimmune, and Chugai Pharma USA but has received no personal fees or personal compensation for these consulting activities. All compensation for consulting activities is paid directly to Mayo Clinic. S.J.P. has received a research grant from Alexion Pharmaceuticals for an investigator-initiated study as well as support from the National Institutes of Health (RO1 NS065829-01) and the Guthy Jackson Charitable Foundation for neuromyelitis optica research. A.M. has received research support from MedImmune and Euroimmun. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**Keywords**

autoimmune limbic encephalitis, diagnosis, epilepsy, immunotherapy, paraneoplastic limbic encephalitis, predictive model

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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**Announcements**

# *Epilepsia* – February 2019 – Announcements

### Seizures and Stroke 2019

20–22 February 2019
Gothenburg, Sweden
Website: https://seizuresandstroke.com/

### Cannabinoids in the Treatment of Epilepsy (Cannabinoide in der Epilepsie-Behandlung)

22 February 2019
Freiburg, Germany
Information: https://www.ilae.org/congresses/cannabinoids-in-the-treatment-of-epilepsy

### 3rd ILAE British Branch Epilepsy Neuroimaging Course

28 February–2 March 2019
Chalfont St Peter, UK
Congress website: https://ilaebritish.org.uk/events/3rd-ilae-british-branch-epilepsy-neuroimaging-course/

### EEG & Epilepsy Educational Course by Sándor Beniczky

1–2 March 2019
Kyiv, Ukraine
Website: http://ulae.org.ua/index.php/en/congresses/future-events

### 5th East Mediterranean Epilepsy Congress

7–9 March 2019
Marrakech, Morocco
Website: http://www.epilepsycongress.org/emec/

### 20th Joint Annual Conference of the Indian Epilepsy Society and Indian Epilepsy Association (ECON 2019)

8–10 March 2019
Lutyen's Delhi, New Delhi, India
http://www.econ2019.org/

### EEG in the First Year of Life – From newborn to toddler

25–28 March 2019
Cambridge, UK
Information: https://www.ilae.org/congresses/eeg-in-the-first-year-of-life

### 13th World Congress on Controversies in Neurology (CONy)

4–7 April 2019
Madrid, Spain
Congress website: http://www.comtecmed.com/cony/2019/

### EEG in Status Epilepticus and on the Intensive Care Unit Teaching Course. ILAE British Branch

6 April 2019
London, UK
https://ilaebritish.org.uk/events/eeg-in-status-epilepticus-and-on-the-intensive-care-unit/

### 7th London-Innsbruck Colloquium on Status Epilepticus & Acute Seizures

7–9 April 2019
London, UK
Congress website: https://statusepilepticus.eu/index.php

### 6th Residential International Course on Drug Resistant Epilepsies

5–11 May 2019
Rome, Italy
More information: https://www.ilae.org/congresses/6th-residential-international-course-on-drug-resistant-epilepsies

### Annual Meeting of the Austrian and German Societies for Epileptology and the Swiss Epilepsy League ("Dreilaendertagung")

8–11 May 2019
Basel, Switzerland
https://www.epilepsie-tagung.de/

### Joint British and Danish ILAE British Advanced Epilepsy Meeting: Channelopathies and Neurosurgery

9–10 May 2019
Copenhagen, Denmark
Information: https://www.ilae.org/congresses/joint-british-and-danish-ilae-british-advanced-epilepsy-meeting-channelopathies-and-neurosurgery

### EAN Spring School 2019

9–11 May 2019
Website and application forms: https://www.ean.org/Spring-School.2711.0.html

### 3rd International Training Course on Neuroimaging of Epilepsy

16–19 May 2019
Montreal, Quebec, Canada
More information: https://www.ilae.org/congresses/3rd-international-training-course-on-neuroimaging-of-epilepsy

### 12th International Epilepsy Colloquium (IEC): Treatment challenges in pediatric & adolescent epilepsies

26–28 May 2019
Lyon, France
Congress website: http://www.epilepsy-colloquium2019.com/

### 23rd Korean Epilepsy Congress (KEC)

15–16 June 2019
Seoul Dragon City, South Korea
Information: https://www.ilae.org/congresses/23rd-korean-epilepsy-congress-2019-kec

### XV Workshop on Neurobiology of Epilepsy (WONOEP 2019)

16–20 June 2019
Ayutthaya, Thailand
Satellite session of the 33rd IEC: http://internationalepilepsycongress.org/wonoep

### 33rd International Epilepsy Congress

22–26 June 2019
Bangkok, Thailand
Website: http://internationalepilepsycongress.org/

### 18th WSSFN Biennial Meeting of the World Society for Stereotactic and Functional Neurosurgery

24–27 June 2019
New York City, NY USA
Congress website: https://wssfn-congress.org/2019#.W_1WieJReUk

### 5th Congress of the European Academy of Neurology (EAN)

29 June–2 July 2019
Oslo, Norway
Bursaries available, see congress website: https://www.ean.org/oslo2019/5th-Congress-of-the-European-Academy-of-Neurology-Oslo-2019.3649.0.html

### 2019 Advanced San Servolo Epilepsy Course

7–18 July 2019
San Servolo, Venice, Italy
Information and application: https://www.ilae.org/congresses/2019-advanced-san-servolo-epilepsy-course

## 13th Baltic Sea Summer School on Epilepsy (BSSSE 13)

18–24 August 2019
Rostock, Germany
Information & application: https://www.ilae.org/congresses/13th-baltic-sea-summer-school-on-epilepsy-bssse-13

## 4th African Epilepsy Congress

22–24 August 2019
Kampala, Uganda
Details and website coming soon!

## 5th Summer School on Imaging in Epilepsy (SuSIE)

25–28 August 2019
Bochum, Germany
Website: http://www.imaging-in-epilepsy.org/

## 2nd International Congress on Mobile Devices and Seizure Detection in Epilepsy

6–7 September 2019
Lausanne, Switzerland
http://www.mhsdepilepsy2019.com/

## ILAE British Branch 17th SpR Epilepsy Teaching Weekend

14-15 September 2019
Oxford, UK.
http://www.epilepsyteachingweekend.com/

## Introduction to Neuropsychological Methods in the Diagnosis and Treatment of People with Epilepsy

18–22 September 2019
Hanoi, Vietnam
Information: https://www.ilae.org/congresses/introduction-to-neuropsychological-methods-in-the-diagnosis-and-treatment-of-people-with-epilepsy

## European Congress of NeuroRehabilitation 2019 (ECNR)

9–12 October 2019
Budapest, Hungary
https://www.ecnr-congress.org/

## EAN Autumn School 2019

17–20 October 2019
Loutraki, Greece
https://www.ean.org/Autumn-School.3752.0.html