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GRAY MATTERS

Commentary

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Commentary on Nóbrega-Jr et al. "Mesial temporal lobe epilepsy with hippocampal sclerosis is infrequently associated with neuronal antibodies"

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Drug-resistant mesial temporal lobe epilepsy involving hippocampal sclerosis (MTLE-HS) is a common neurological disease at tertiary epilepsy centers. It is of great interest to identify the underlying etiology of MTLE-HS (eg, autoimmune), so as to treat patients adequately (eg, immunosuppression) without time delay. Accumulating evidence suggests that autoimmune encephalitis within the limbic system (limbic encephalitis [LE]) is an underestimated and increasing cause of MTLE-HS.[1–3] In line with those studies, the study of Nóbrega-Jr et al[4] questioned the frequency of neuronal antibodies in MTLE-HS as a parameter to determine which epilepsy patients might retrospectively have had an underlying autoimmune disease etiology and might profit from immunotherapy. To apply Graus' criteria to these patients is not trivial, as some patients with definitive LE do not present any association with neuronal antibodies.[5]

The study of Nóbrega-Jr et al[4] is an important contribution to this challenging topic, as it encompasses the second largest group of MTLE-HE patients (n = 100; Table 1) to investigate this important, controversial issue in clinical epileptology (for studies see Table 1),[6–8] considering the frequency of neuronal antibodies in MTLE-HS and the role of these neuronal antibodies play in an autoimmune origin. Nóbrega-Jr et al[4] report a low antibody frequency of three in 100 (3%) patients with only glutamic acid decarboxylase 65 (GAD65) antibodies in their MTLE-HS Brazilian patients who presented no symptoms and signs of autoimmune encephalitis; this frequency lies within the lower range of those reported by other studies of MTLE-HS patients (ranging from 0% to 23%[6–8]; Table 1).

However, after carefully studying their study design, I have some potential explanations for their findings; namely, their MTLE-HS patients' relatively low neuronal antibody rate suggesting autoimmunity.

First, the late testing of neuronal antibodies after decades of disease duration (mean = 27 years in the Nóbrega-Jr et al[4] study) could reveal a negative antibody result that might have been positive at the disease's initial presentation and during certain time periods within the disease course. LE could be one cause of hippocampal sclerosis leading to a chronic epileptic disease state potentially accompanied by a relapsing-remitting course of detectable inflammation and neuronal antibodies years after the disease onset, as in GAD65 patients.[9] Only four patients were examined whose MTLE onset was relatively recent (≤6 years); thus, an early phase of the disease course in these patients might be encountered with a greater probability of obtaining detectable, positive neuronal antibody results. Thus, it is very likely that a higher frequency of neuronal antibodies in MTLE-HS patients would have been detected if neuronal antibodies had been tested earlier in the disease course. In addition, the main group comprises early onset MTLE-HS patients, containing a large group of febrile-seizure patients in whom autoimmunity's later occurrence is unclear.[10] Thus, early onset[6,8] and late onset MTLE-HS such as reported by Vanli-Yavuz[7] could differ fundamentally in neuronal antibody frequency, and further large-scale studies are needed to determine more exactly the frequency of antibodies and possible underlying autoimmunity.

Second, another critical issue in this study concerns the type of autoantibodies investigated. Frequently occurring neuronal autoantibodies were assessed, such as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid B receptor, *N*-methyl-D-

TABLE 1 Studies of MTLE-HS patients and associated neuronal antibody frequency

Patients, n	Gender, females	Age of patients, y	Epilepsy duration, y	Investigations	Type of antibodies in peripheral blood	Antibody frequency	References
111	66	38 ± 9.9	9 ± 7.5	1.5-T MRI, EEG, NPT	NMDA NR1/NR2 subunits, AMPA GluR1/2 subunits, LGI1, CASPR2, glycin, GABA-A	25/111 (23%)	Vanli-Yavuz 2016[7]
100	55	41.2 ± 11.9	27.2 ± 13.4	1.5-T MRI, EEG	NMDA, CASPR2, LGI1, AMPA GluR1/2 subunits, GAD65	3/100 (3%)	Nóbrega-Jr 2018[4]
26	–	32.6 ± 9.4	16 (10.5–18.5)	1.5-T MRI, EEG, NPT	NMDA, AMPA, LGI1 CASPR2, glycin, VGKC, GAD65	6/26 (23%)	Ekizoglu 2014[8]
15	9	29.5 ± 7.8	18.9 ± 8	1.5/3-T MRI, PET, SPECT, NPT, EEG	NMDA, LGI1, CASPR2, AMPA, GABA-B, GAD65	0/15 (0%)	Tezer 2018[6]

AMPA, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CASPR2, contactin-associated protein-like 2; EEG, electroencephalography; GABA, γ-aminobutyric acid; GAD65, glutamic acid decarboxylase 65-kDa isoform; GluR, glutamate receptor; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging; MTLE-HS, mesial temporal lobe epilepsy involving hippocampal sclerosis; NMDA, *N*-methyl-D-aspartate receptor; NPT, neuropsychological testing; PET, positron emission tomography; SPECT, single photon emission computed tomography; VGKC, voltage-gated potassium channel; y, years; -, data not shown.

aspartate receptor, and GAD65; however, major groups of antibodies were not determined, such as paraneoplastic antibodies against intracellular antigens. To identify a naturalistic pattern of neuronal antibody occurrence, a broader panel of antibodies should be investigated in future studies.

Third, only samples of peripheral blood and not of the cerebrospinal fluid (CSF) were tested. As a CSF examination is compulsory to detect an inflammatory or autoimmune process in the CSF, no statements regarding an ongoing autoimmune process in their patients can be made with certainty.

Fourth, neuropsychological testing might have changed the assumed diagnosis of MTLE-HS to LE according to the Graus criteria,[5] as subtle changes in memory performance (such as accelerated long-term forgetting) are occasionally only detectable over the long term in LE, often associated with no antibodies.[11] However, this is a complicated issue, as it is tricky to distinguish LE patients from those with temporal lobe epilepsy not principally of autoimmune origin, as patients with hippocampal sclerosis often present memory deficits independent of hippocampal sclerosis etiology.

To conclude, this study is useful and essential to furthering our knowledge in neuronal antibody-associated MTLE-HS research, but the necessary steps must be taken to broaden our cross-sectional perspective of the neuronal antibody frequency in several MTLE-HS subgroups.

DISCLOSURE

The author has no conflicts of interest to report. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Announcements

Epilepsia – December 2018 – Announcements

9th EPODES Advanced I

21–25 January 2018
Brno, Czech Republic
Congress website: http://www.ta-service.cz/epodes2019/

Seizures and Stroke 2019

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

Cannabinoids in the Treatment of Epilepsy

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

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
http://www.epilepsycongress.org/emec/

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

8–10 March 2019
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://comtecmed.inwise.net/CONyCongress2019

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
IRCCS, 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/

3rd International Training Course on Neuroimaging of Epilepsy

16–19 May 2019
Montreal, Quebec, Canada
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
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XV Workshop on Neurobiology of Epilepsy (WONOEP 2019)

16–20 June 2019
Ayutthaya, Thailand
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33rd International Epilepsy Congress

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Bangkok, Thailand
Website: http://internationalepilepsycongress.org/

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San Servolo, Venice, Italy
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4th African Epilepsy Congress

22–24 August 2019
Kampala, Uganda
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5th Summer School on Imaging in Epilepsy (SuSIE)

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