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Registry-Based Phenotyping to Improve the Diagnosis of Autoimmune Encephalitis

Seizure Semiology in Antibody-Associated Autoimmune Encephalitis

Kaaden T, Madlener M, Angstwurm K, Bien CG, Bogarin Y, Doppler K, Finke A, Gerner ST, Reimann G, Häusler M, Handreka R, Hellwig K, Kaufmann M, Kellinghaus C, Koertvelyessy P, Kraft A, Lewerenz J, Menge T, Paliantonis A, von Podewils F, Prüss H, Rauer S, Ringelstein M, Rostásy K, Schirotzek I, Schwabe J, Sokolowski P, Suesse M, Sühs K-W, Surges R, Tauber SC, Thaler F, Bergh FT, Urbanek C, Wandinger K-P, Wildemann B, Mues S, Zettl U, Leypoldt F, Melzer N, Geis C, Malter M, Kunze A; The Generate Study Group. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(6):e200034. doi:10.1212/NXI.0000000000200034

Background and Objectives: To assess seizure characteristics in antibody (ab)-associated autoimmune encephalitis (ab +AE) with the 3 most prevalent abs against N-methyl-D-aspartate receptor (NMDAR), leucine rich glioma-inactivated protein 1 (LGI1), and glutamic acid decarboxylase (GAD). Methods: Multicenter nationwide prospective cohort study of the German Network for Research in Autoimmune Encephalitis. Results: Three hundred twenty patients with ab + AE were eligible for analysis: 190 NMDAR+, 89 LGI1+, and 41 GAD+. Seizures were present in 113 (60%) NMDAR+, 69 (78%) LGI1+, and 26 (65%) GAD+ patients and as leading symptoms for diagnosis in 53 (28%) NMDAR+, 47 (53%) LGI+, and 20 (49%) GAD+ patients. Bilateral tonic-clonic seizures occurred with almost equal frequency in NMDAR+ (38/51, 75%) and GAD+ (14/20, 70%) patients, while being less common in LGI1+ patients (27/59, 46%). Focal seizures occurred less frequently in NMDAR+(67/113; 59%) than in LGI1+ (54/69, 78%) or in GAD+ patients (23/26; 88%). An aura with deja-vu phenomenon was nearly specific in GAD+ patients (16/20, 80%). Faciobrachial dystonic seizures (FBDS) were uniquely observed in LGI1+ patients (17/59, 29%). Status epilepticus was reported in one-third of NMDAR+ patients, but only rarely in the 2 other groups. The occurrence of seizures was associated with higher disease severity only in NMDAR+ patients. Discussion: Seizures are a frequent and diagnostically relevant symptom of ab + AE. Whereas NMDAR+ patients had few localizing semiological features, semiology in LGI1+ and GAD+ patients pointed toward a predominant temporal seizure onset. FBDS are pathognomonic for LGI1 + AE. Status epilepticus seems to be more frequent in NMDAR + AE.

Epileptic Phenotypes in Autoimmune Encephalitis: From Acute Symptomatic Seizures to Autoimmune-Associated Epilepsy

Matricardi S, Casciato S, Bozzetti S, Mariotto S, Stabile A, Freri E, Deleo F, Sartori S, Nosadini M, Pappalardo I, Meletti S, Giovannini G, Zucchi E, Di Bonaventura C, Di Gennaro G, Ferrari S, Zuliani L, Zoccarato M, Vogrig A, Lattanzi S, Michelucci R, Gambardella A, Ferlazzo E, Fusco L, Granata T, Villani F; On behalf of the Immune Epilepsies Study Group of the Italian League Against Epilepsy. *J Neurol Neurosurg Psychiatry*. 2022;93(11). doi:10.1136/jnnp-2022-329195

Objective: To describe the clinical and paraclinical findings, treatment options and long-term outcomes in autoimmune encephalitis (AE), with a close look to epilepsy. Methods: In this retrospective observational cohort study, we enrolled patients with new-onset seizures in the context of AE. We compared clinical and paraclinical findings in patients with and without evidence of antibodies. Results: Overall, 263 patients (138 females; median age 55 years, range 4–86) were followed up for a median time of 30 months (range 12–120). Antineuronal antibodies were detected in 63.50%. Antibody-positive patients had multiple seizure types ($p = 0.01$) and prevalent involvement of temporal regions ($p = 0.02$). A higher prevalence of episodes of SE was found in the antibody-negative group ($p < 0.001$). Immunotherapy was prescribed in 88.60%, and effective in 61.80%. Independent predictors of favourable outcome of the AE were early immunotherapy ($p < 0.001$) and the detection of antineuronal surface antibodies ($p = 0.01$). Autoimmune-associated epilepsy was the long-term sequela in 43.73%, associated with cognitive and psychiatric disturbances in 81.73%. Independent predictors of developing epilepsy were difficult to treat seizures at onset ($p = 0.04$), a high number of antiseizure medications ($p < 0.001$), persisting interictal epileptiform discharges at follow-

up ($p < 0.001$) and poor response to immunotherapy during the acute phase ($p < 0.001$). Conclusions: The recognition of seizures secondary to AE represents a rare chance for aetiology-driven seizures management. Early recognition and treatment at the pathogenic level may reduce the risk of long-term irreversible sequelae. However, the severity of seizures at onset is the major risk factor for the development of chronic epilepsy. This study provides class IV evidence for management recommendations.

Commentary

The neurology community has come a long way since the characterization of N-methyl-D-aspartate (NMDA) receptor antibodies in 2008,[1] which started the wave of surface neural autoantibody discovery and phenotypic characterization of antibody-mediated neurologic syndromes. For years, many autoimmune neurology publications have arisen from single centers and focused on individual antibodies, hindering utility to a clinician faced with a phenotypic presentation, prior to antibody results which can often take weeks to return. Thankfully, efforts to systematically phenotype large multicenter encephalitis registries are finally bearing fruit and can now help a clinician eager to understand better what clinical characteristics are unique to autoimmune encephalitis.

One such study harnessed the GENERATE registry, a multicenter German study underway since 2004, and pooled data spanning 12 years, over 40 centers, reporting on the seizure characteristics of 208 patients with acute symptomatic seizures out of 320 patients with antibody-mediated encephalitis (NMDA-receptor, leucinerich glioma-inactivated protein 1 [LGI1], and high titer GAD65 antibodies).[2] Specifically, this report aims to answer the following question: what are the electroclinical characteristics of acute symptomatic seizures associated with the most common antibody-mediated encephalitides? The authors found that seizures were often a presenting, initially isolated feature, with LGI1 antibodies. Seizure semiology segregated according to antibody: motor onset seizures were more common with NMDA-R antibodies, while impaired awareness was more common with LGI1 antibodies, and autonomic seizures occurred with both LGI1 and GAD65 antibodies. Focal aware seizure semiology characteristic of GAD65 antibodies included déjà vu and other "cognitive" symptoms. Meanwhile they confirmed the pathognomonic association of faciobrachial dystonic seizures with LGI1 antibodies. Lastly, tonic–clonic seizures were rare in the case of LGI1 antibodies. While the majority of each antibody group did exhibit acute symptomatic seizures, many patients without seizures did have an abnormal EEG with features indicating a risk for seizures. Semiologic features were obtained through report from each site investigators, rather than through prospective structured questionnaires. Interestingly, the previously reported associated with musicogenic epilepsy[3] was not seen in this large registry, possibly due to underreporting by each site's investigator. Seizures were associated with worse disease severity in the group with NMDA-R antibodies. In this study, the authors did not task themselves with examining the risk of autoimmune-associated epilepsy.

Another study leveraged an ongoing cohort established by the Italian League Against Epilepsy in 2010, spanning 10 years, 34 centers, and went further to examine 263 patients with either antibody-positive or antibody-negative probable autoimmune encephalitis with acute symptomatic seizures.[4] The diagnostic definition of antibody-negative autoimmune encephalitis was rigorous and required at least 2 pan-neurologic symptoms and 1 ancillary marker of brain autoimmunity. The antibody-positive group included not only NMDA-R, LGI1, GAD65 but also CASPR2, GABA-A, GABA-B, glycine-receptor, and onconeural antibodies. The authors found that extratemporal semiology was more common in the antibody-negative group, but concluded that this was likely driven by the high frequency of temporal lobe semiology in the LGI1 antibody group. Unlike the GENERATE registry publications, there were no further details on semiology beyond the temporal/extratemporal categorization. This cohort also provides new data on predictors of autoimmune-associated epilepsy (i.e., persistent seizures past the autoimmune encephalitis phase), which occurred in almost half of patients in this series. Difficult to treat seizures at onset, poor response to immunotherapy, high number of anti-seizure medications, and persistent interictal epileptiform discharges at the follow-up EEG all predicted ongoing seizures, but not time to immunotherapy, indicating that the severity of disease bears a large role in the outcome. Interestingly, brain atrophy, including medial temporal atrophy, did not predict epilepsy, which could mean that structural injury alone cannot account for ongoing seizures. The rates of ongoing seizures (i.e., autoimmune associated epilepsy) in this broad cohort was high (almost half of patients) and was most common among antibody-negative encephalitis.

Both of these studies are impressive in terms of the sheer number of patients analyzed, spanning many years and centers. Some of the conclusions reinforce what we already knew (e.g., faciobrachial dystonic seizures indicate LGI1 antibodies), but novel findings include the association of limbic semiology with GAD65 antibodies, motor onset seizures in NMDA-receptor encephalitis, and extratemporal semiology in antibody-negative autoimmune encephalitis. The high frequency of autoimmune-associated epilepsy in the Italian cohort study contrasts with prior publications quoting rates of autoimmune-associated epilepsy as low as 1% in one Dutch cohort of surface antibody-mediated encephalitis[5] and up to one-third in a broader cohort of antibody-mediated encephalitis.[6] The inclusion of cases treated from 2010 onward, perhaps when aggressive escalation of immunotherapy was less

common, and inclusion of antibody-negative encephalitic cases may account for the different rates.

These registries mark an important step toward the next era of encephalitis research—multicenter, registry-based research including multiple types of antibodies along with antibody-negative probable autoimmune encephalitis. This phenotypically oriented approach is more easily translatable to clinical practice than antibody-centric publications, given that the diagnostic process and decision-making about empiric immunotherapy is more often done days to weeks prior to antibody testing results becoming available.

Many Questions Remain Though

How do acute symptomatic seizures from autoimmune encephalitis differ from that in other nonautoimmune brain conditions? Many patients may not initially have a definite autoimmune phenotype, and the epileptologist may want to know what electroclinical features differentiate not only one antibody from another (like the GENERATE registry attempts to discuss), but autoimmune from other nonautoimmune conditions. Judicious use of control groups will enable these future analyses.

Are there more *specific* semiologic and EEG characteristics suggestive of autoimmune encephalitis? Is a certain seizure frequency (e.g., daily as opposed to weekly) suggestive? What about multifocal seizure types? Prospective structured data collection will be required to answer these phenotyping questions in more detail.

Claude Steriade
New York University

ORCID iD

Claude Steriade https://orcid.org/0000-0001-6799-9005

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091-1098.
2. Kaaden T, Madlener M, Angstwurm K, et al. Seizure semiology in antibody-associated autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2022;9(6):e200034.
3. Smith KM, Zalewski NL, Budhram A, et al. Musicogenic epilepsy: expanding the spectrum of glutamic acid decarboxylase 65 neurological autoimmunity. *Epilepsia*. 2021;62(5):e76-e81.
4. Matricardi S, Casciato S, Bozzetti S, et al. Epileptic phenotypes in autoimmune encephalitis: from acute symptomatic seizures to autoimmune-associated epilepsy. *J Neurol Neurosurg Psychiatry*. 2022.
5. de Bruijn M, van Sonderen A, van Coevorden-Hameete MH, et al. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis. *Neurol*. 2019;92(19):e2185-e2196.
6. Falip M, Jaraba S, Rodríguez-Bel L, et al. Seizures and epilepsy of autoimmune origin: a long-term prospective study. *Seizure*. 2020; 81:157-165.