Neuronal antibodies in adult patients with new-onset seizures: A prospective study

Johan Zelano1,2 | Markus Axelsson1,2 | Radu Constantinescu1,2 | Clas Malmeström1,2,3 | Eva Kumlien4

Abstract

Objectives: Immunotherapy in addition to antiepileptic drugs can improve seizure freedom rates in autoimmune epilepsy, highlighting the importance of early diagnosis. A diagnosis of autoimmune epilepsy can be supported by presence of serum antibodies to neuronal antigens. We asked how often neuronal antibodies are found in the serum of unselected adult patients with new-onset seizures and whether such testing could improve detection of autoimmune epilepsy.

Material and Methods: We included 44 patients over the age of 25 presenting after at least one unprovoked seizure to the Neurology Clinic at Sahlgrenska University Hospital, Gothenburg, Sweden. The median time between the first-ever seizure in life and the serum sampling was 50 days (range 22–11,000). Antibody testing in serum was performed according to the manufacturer’s instructions. The patients were followed for at least 1 year.

Results: Epilepsy could be diagnosed already at the first visit in 21/44 patients (47.7%). Two patients (4.5%) were positive for neuronal antibodies: one against contactin-associated protein 2 (CASPR-2) and one against glutamate acid decarboxylase (GAD). Three patients (6.7%) displayed very weak immunoreactivity that was deemed clinically insignificant. One of the antibody-positive patients had only a single seizure. The other had a focal cortical dysplasia and was seizure-free on levetiracetam. None of the five patients with antibodies or immunoreactivity displayed any feature of autoimmune epilepsy.

Conclusions: We conclude that indiscriminate testing in patients presenting to a first seizure clinic with new-onset seizures or epilepsy is unlikely to improve detection of autoimmune epilepsy.

Keywords

autoimmune, epilepsy, seizure

1 INTRODUCTION

Autoimmune epilepsy refers to epilepsy resulting from immune-driven processes in the brain and is a recognized etiological category in the International League Against Epilepsy (ILAE) classifications of epilepsies (Scheffer et al., 2017). The clinical spectrum is probably wide, ranging from limbic encephalitis with prominent psychiatric symptoms to epilepsy without other symptoms than seizures.
Nonparaneoplastic cases are more common than paraneoplastic ones, and autoimmune epilepsy has been suggested to account for up to 20% of epilepsy of unknown etiology (Bien & Holtkamp, 2017; Dubey, Alqallaf, et al., 2017; Irani, Bien, & Lang, 2011).

A diagnosis of autoimmune epilepsy can be supported by presence of neuronal antibodies in serum, which are most commonly directed against particular neuronal antigens (Irani et al., 2011). Antibody testing is usually prompted by clinical suspicion based on high seizure frequency, simultaneous onset of psychiatric symptoms, or particular seizure types like faciobrachial dystonic seizures. In cases of immune-mediated epilepsy, immunotherapy in addition to antiepileptic drugs can improve seizure freedom rates, highlighting the importance of early diagnosis (Feyissa, Lopez Chiriboga, & Britton, 2017).

Studies on the prevalence of neuronal antibodies in patients with epilepsy of unknown etiology have yielded somewhat conflicting results. In two large epilepsy cohorts, neuronal antibodies were detected in serum in approximately one tenth of cases (Brenner et al., 2013; Suleiman et al., 2013). A higher rate was described in a recent prospective study, where investigators found antibody positivity in serum of more than one third (13/35) of adult patients with new-onset epilepsy and an association between reduction in seizure frequency and immunotherapy (Dubey, Alqallaf, et al., 2017). In a more selected patient group with temporal lobe epilepsy, serum antibodies were found in 5.5% and a response to immunotherapy measured as a >50% reduction in seizures was seen in half of the antibody-positive patients (Elisak et al., 2018).

Given the possibility of treatment response to immunotherapy, autoimmune epilepsy should ideally be found as early as possible. The potential of early identification by antibody testing was recently evaluated in a cohort of children with new-onset seizures, in which very low rates of serum antibodies were detected (Garcia-Tarodo et al., 2018). We are unaware of any study investigating the potential of early antibody testing to identify autoimmune epilepsy in adults. We therefore asked how often neuronal antibodies are found in the serum of unselected adult patients with new-onset seizures and whether the presence of antibodies was associated with detection of autoimmune epilepsy.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and cohort

From June 2016, adult patients with new-onset seizures, seen at the Department of Neurology at Sahlgrenska University Hospital in Gothenburg, Sweden, were invited to participate in a prospective observational study evaluating biomarkers and quality of life in adult-onset epilepsy. Recruitment was not systematic, and no screening log was kept. Sahlgrenska University Hospital is the largest neurological service in Gothenburg (population 650,000), providing secondary and tertiary epilepsy care. Most patients were seen within the setting of a “first seizure” clinic, where follow-up is provided to patients referred from emergency departments. Inclusion criteria were a first unprovoked seizure after the age of 25, as assessed by the clinician at the visit (since the purpose was to test clinical utility). Exclusion criteria were progressive causes of the seizure-like tumor or dementia and inability to give informed consent. Until December 2017, 44 patients had been included.

### 2.2 | Antibody testing

Serum samples were collected at recruitment and stored in an approved storage facility (biobank, registration no 532) until analysis. Antibody analysis was performed with indirect immune fluorescence BIOCHIP encephalitis Mosaic (glutamate receptor type NMDA, glutamate receptor type AMPA ½, LGI1, CASPR2, GABA-B receptors, and DPPX) and Euroline immunoblot (Tr, GAD65, Zic4, Titin, SOX1, Recoverin, Hu, Yo, Ri, Ma2/Ta, CV2, Amphiphysin), on automated Euroblot-One instrument and results scanned EUROLineScan. Positive samples proceeded to indirect immunofluorescences on pri‐

### 2.3 | Clinical characteristics

At inclusion and at least 1 year after the collection of serum samples, patients were contacted by telephone or interviewed at a clinic visit and information was collected from the answers and the electronic medical record into a predefined clinical report form. Epilepsy was categorized according to a simplified scheme as either structural/metabolic or unknown cause. Imaging with CT is typically done before the patient is seen and MRI performed if an epilepsy cause is not identified on CT.

### 2.4 | Statistical analyses

Data are expressed as median and range for continuous variables and frequencies for categorical variables. All analyses were performed using IBM SPSS version 23.

### 2.5 | Ethics

All patients provided written informed consent. The regional ethical review board of Gothenburg approved the study, approval no 844-15.

## 3 | RESULTS

### 3.1 | Cohort

The study cohort consisted of 44 patients seen in a first seizure clinic. Demographic and clinical characteristics are presented in Table 1. Approximately half of the patients did not meet epilepsy criteria, meaning that they had had only one seizure and a seizure recurrence risk estimated below 60% by the treating physician at the time of the serum sampling. The median time between the first ever seizure in life and the serum sampling was 50 days (range 22–11,000 days, the upper range being influenced by one patient having had a childhood seizure). Epilepsy was diagnosed already at the first visit in 21 patients.
3.2 | Antibody testing

Two patients (4.5%) were positive for neuronal antibodies: one against contactin-associated protein 2 (CASPR-2) and one against glutamate acid decarboxylase (GAD). Three patients (6.7%) displayed very weak immunoreactivity that was deemed clinically insignificant for Sox-1 or Yo.

3.3 | Seizure outcome

No patient with antibody reactivity was lost to follow-up. Clinical course of all patients with neuronal antibodies or weak immunoreactivity is presented in Table 2. The patient with CASPR2 antibodies did not have any seizure relapse after the first seizure. Screening for malignancy revealed a localized asymptomatic sigmoid carcinoma. The patient with GAD antibodies had a cortical dysplasia on MRI, negative work-up for malignancy, and remained seizure-free on a low dose of levetiracetam. No patients with unspecific immunoreactivity had further tonic–clonic seizures; one patient had only a single seizure, one was diagnosed with juvenile myoclonic epilepsy (JME) based on emergence of myoclonia and EEG-findings, and one had poststroke epilepsy. Both patients with epilepsy were seizure-free on levetiracetam and had no clinical features suggestive of autoimmune epilepsy.

TABLE 1  Study cohort

| Sex          | n      | %    |
|--------------|--------|------|
| Male         | 21     | 47.7 |
| Female       | 23     | 52.3 |

| Age          | n      | %    |
|--------------|--------|------|
| 25–40        | 16     | 36.4 |
| 41–55        | 12     | 27.3 |
| 56–70        | 7      | 15.9 |
| 71–85        | 9      | 20.5 |

| Clinical     | n      | %    |
|--------------|--------|------|
| No epilepsy  | 23     | 52.3 |
| Epilepsy     | 21     | 47.7 |

| Etiology (n = 21) | n  | %   |
|-------------------|----|-----|
| Structural/metabolic | 8  | 38.1|
| Unknown cause     | 13 | 61.9|

| Imaging (CT or MRI) | n | %  |
|---------------------|---|----|
|                      | 44 | 100|

| Result (n = 44) | n  | %   |
|-----------------|----|-----|
| Normal          | 31 | 70.5|
| Previous stroke | 7  | 15.9|
| Other           | 6  | 13.6|

Note: Demographics, clinical characteristics, and test results available at enrollment in the study cohort.

TABLE 2  Patients with neuronal antibodies or weak immunoreactivity

| Patient no | Antibody | Malignancy | Diagnosis at follow-up | Further seizures | EEG | Imaging at follow-up | Clinical features at follow-up | Medically refractory |
|------------|----------|------------|------------------------|-------------------|-----|----------------------|-------------------------------|---------------------|
| 1          | GAD      | No         | Normal                 | No                | Normal | DWI: small silent ischemia | Infarction                   | No                  |
| 2          | CASPR-2  | No         | Normal                 | No                | Normal | N/A                  | N/A                           | No                  |
| 3          | Sox1     | No         | Normal                 | No                | Normal | PSW                  | N/A                           | No                  |
| 4          | Sox1     | No         | Normal                 | No                | Normal | PSW                  | N/A                           | No                  |
| 5          | Yo       | Yes        | Infarction             | No                | N/A   | PSW                  | N/A                           | No                  |

Note: Demographics, clinical characteristics, and test results available at enrollment in the study cohort.
CONFLICT OF INTEREST

JZ has received consultancy fee from the Swedish Medical Products Agency and writers honoraria from the journal Neurology in Sweden, and is as an employee of Sahlgrenska university hospital investigator/subinvestigator in clinical trials sponsored by GW Pharma, SK life science, and Bial (no personal compensation). MA has received compensation for lectures and/or advisory boards from Biogen, Genzyme, and Novartis. CA has received honoraria for lectures and advisory boards from Biogen and Novartis.

DATA AVAILABILITY STATEMENT

Some anonymized data that support the findings of this study can be shared by the corresponding author upon request. All data are not publicly available due to confidentiality/privacy restrictions.

ORCID

Johan Zelano https://orcid.org/0000-0001-9445-4545
Markus Axelsson https://orcid.org/0000-0003-2036-4007
Radu Constantinescu https://orcid.org/0000-0001-5408-5167

REFERENCES

Aykutlu, E., Baykan, B., Gurses, C., Gokyigit, A., & Saruhan-Direskeneli, G. (2005). No association of anti-GM1 and anti-GAD antibodies with juvenile myoclonic epilepsy: A pilot study. Seizure, 14(5), 362-366. https://doi.org/10.1016/j.seizure.2005.04.009
Bien, C. G., & Holtkamp, M. (2017). “Autoimmune epilepsy”: Encephalitis with autoantibodies for epileptologists. Epilepsy Currents, 17(3), 134-141. https://doi.org/10.5698/1535-7511.17.3.134
Brenner, T., Sills, G. J., Hart, Y., Howell, S., Waters, P., Brodie, M. J., ..., Lang, B. (2013). Prevalence of neurologic autoimmune epilepsies in cohorts of patients with new and established epilepsy. Epilepsia, 54(6), 1028-1035. https://doi.org/10.1111/epi.12127
Dubey, D., Alqallaf, A., Hays, R., Freeman, M., Chen, K., Ding, K., ..., Vernino, S. (2017). Neurological autoantibody prevalence in epilepsy of unknown etiology. JAMA Neurology, 74(4), 397-402. https://doi.org/10.1001/jamaneuro.2016.5429
Dubey, D., Singh, J., Britton, J. W., Pittcock, S. J., Flanagan, E. P., Lennon, V. A., ... McKeon, A. (2017). Predictive models in the diagnosis and treatment of autoimmune epilepsy. Epilepsia, 58(7), 1181-1189. https://doi.org/10.1111/epi.13797
Elisak, M., Krysl, D., Hanzalova, J., Volna, K., Bien, C. G., Leypoldt, F., & Marusic, P. (2018). The prevalence of neural antibodies in temporal lobe epilepsy and the clinical characteristics of seropositive patients. Seizure, 63, 1-6. https://doi.org/10.1016/j.seizure.2018.09.009
Feyissa, A. M., Lopez Chiriboga, A. S., & Britton, J. W. (2017). Antiepileptic drug therapy in patients with autoimmune epilepsy. Neurology - Neuroimmunology Neuroinflammation, 4(4), e353. https://doi.org/10.1212/NXI.0000000000000353
Garcia-Tarodo, S., Datta, A. N., Ramelli, G. P., Marechal-Rouiller, F., Bien, C. G., & Korff, C. M. (2018). Circulating neural antibodies in unselected children with new-onset seizures. European Journal of Paediatric Neurology, 22(3), 396-403. https://doi.org/10.1016/j.ejpn.2017.12.007

ACKNOWLEDGMENTS

Storage of samples was kindly provided by the Department of Neurochemistry, Sahlgrenska hospital.
Graus, F., Titulaer, M. J., Balu, R., Benseler, S., Bien, C. G., Cellucci, T., ... Dalmau, J. (2016). A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology, 15(4), 391–404. https://doi.org/10.1016/S1474-4422(15)00401-9

Irani, S. R., Bien, C. G., & Lang, B. (2011). Autoimmune epilepsies. Current Opinion in Neurology, 24(2), 146–153. https://doi.org/10.1097/WCO.0b013e3283446f05

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., ... Zuberi, S. M. (2017). ILAE classification of the epilepsies: Position paper of the ILAE commission for classification and terminology. Epilepsia, 58(4), 512–521. https://doi.org/10.1111/epi.13709

Suleiman, J., Wright, S., Gill, D., Brillot, F., Waters, P., Peacock, K., ... Lang, B. (2013). Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies. Epilepsia, 54(12), 2091–2100. https://doi.org/10.1111/epi.12405

How to cite this article: Zelano J, Axelsson M, Constantinescu R, Malmström C, Kumlien E. Neuronal antibodies in adult patients with new-onset seizures: A prospective study. Brain Behav. 2019;9:e01442. https://doi.org/10.1002/brb3.1442