



Anti-Neuronal Autoantibodies in Both Drug Responsive and Resistant Focal Seizures with Unknown Cause[☆]



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ARTICLE INFO

Keywords:

autoantibodies
epilepsy of unknown cause
autoimmunity
focal epilepsy
prognosis

ABSTRACT

Background: and Objective Autoimmunity is an emerging field of research in the etiology of different neurological disorders including epilepsy. We aimed to investigate the presence of neuronal autoantibodies in focal epilepsy with unknown cause and their clinical correlates in both drug-responsive and resistant patients.

Method: Between 2009 and 2010 94 patients were prospectively enrolled, had their antibodies tested and clinically followed. An additional 50 age- and gender-matched controls were also tested for antibodies. Age at examination, gender, age at onset, seizure frequency, risk factors, seizure precipitants, and type of seizures were noted. Plasma obtained from patients was frozen at -80°C and analysed for autoantibodies against VGKC-complex, VGCC, GAD, LGI1, CASPR2, NMDA, AMPA and GABAB receptors with immunocytochemistry and radioimmunoassay as required.

Results: Thirteen (13.8%) patients, but none of the controls, had antibodies ($p = 0.003$). Antibodies were directed against the uncharacterized components of VGKC-complex in 5 patients (5.3%), GAD in 4 patients (4.2%), NMDA-R in 1 patient (1%), AMPA-R in 1 patient (1%) and both GAD and VGKC-complex in 2 patients (2.1%). Prognosis of epilepsy, in subsequent follow-up, did not correlate to general presence of anti-neuronal antibodies with slightly more patients with antibodies epilepsy control than without (76.9% vs. 69.1%, not-statistically significant). Three patients with suspected active autoimmunity and epilepsy who were treated, showed a response to treatment with a reduction in the seizure frequency. Although most clinical features were identical between seropositive and seronegative patient groups, seropositive patients were more likely to have inflammatory/autoimmune disorders in their medical history.

Discussion: In keeping with previous studies, we have shown anti-neuronal antibodies in a proportion of focal epilepsy patients. Although autoimmunity might merely occur as a bystander effect in many chronic neurological disorders, association of anti-neuronal antibodies with good response to immunotherapy and coexisting autoimmune disorders suggests that anti-neuronal autoimmunity might participate in seizure formation at least in a subgroup of focal epilepsy patients.

Conclusion: Immunity may play a role in some patients with unknown etiology regardless of prognosis and immunomodulatory treatment may be helpful in seropositive group.

1. Introduction

In recent years there have been significant advances in our understanding of the underlying etiologies of the epilepsies, underpinned by

developments in neuroimaging and genetic testing. The most common etiologies are structural, genetic, metabolic, infectious and immune-related, the last having been recently included (ILAE webpage). However, the underlying causes cannot be determined in

Abbreviations: VGKC, voltage-gated potassium channel; NMDA-R, N-Methyl-D-Aspartate receptor; AMPA-R, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABAB-R, gamma aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; GLY-Rs, glycine receptors; mGluR5, metabotropic glutamate receptor 5; DPPX, dipeptidyl peptidase like protein-6; GABAB-R, gamma aminobutyric acid B receptor; VGCC, voltage gate calcium channel; FBDS, faciobrachial dystonic seizures; CASPR-2, contactin-associated protein 2; AED, anti-epileptic drug; MRI, magnetic resonance imaging; ILAE, International League Against Epilepsy; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; RIA, radioimmunoassay; IVIG, intravenous immune globulin

[☆] The manuscript was presented at the 31st International Epilepsy Congress in 2015.

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<http://dx.doi.org/10.1016/j.epilepsyres.2017.06.008>

Received 18 May 2016; Received in revised form 18 April 2017; Accepted 13 June 2017

Available online 17 June 2017

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approximately 30–60% of patients despite all the advances in the neurological sciences (Wirrell et al., 2011; Kwan and Brodie, 2000).

Recent studies have demonstrated that the immune system has an important role in the etiology of seizures leading to the emergence of a new group of epilepsy, so called ‘autoimmune epilepsy’ (Bien and Scheffer, 2011; Granerod et al., 2010; Irani et al., 2011; Leypoldt et al., 2015; Khawaja et al., 2016). The current recognized clinical syndromes related to serum antibodies to proteins in the central nervous system are limbic encephalitis/encephalopathies or faciobrachial dystonic seizures (FBDS) with antibodies against voltage-gated potassium channel (VGKC)-complex, N-Methyl-D-Aspartate receptor (NMDA-R), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), gamma aminobutyric acid B receptor (GABAB-R) glutamic acid decarboxylase (GAD) and glycine receptors (GLY-Rs) (Brenner et al., 2013; Irani et al., 2008; Irani et al., 2010; Irani et al., 2011; Liimatainen et al., 2010; Majoie et al., 2006; McKnight et al., 2005; Onugoren et al., 2014; Thieben et al., 2004; Vincent et al., 2004). Two recent studies which presented two large unselected cohorts of a new onset epilepsy or epilepsy with a chronic course also showed different types of the above mentioned antibodies (Brenner et al., 2013; Ekizoglu et al., 2014). Brenner and colleagues (Brenner et al., 2013) demonstrated that 11% of patients with established or newly diagnosed generalized or focal epilepsy were seropositive for at least one of the antibodies to VGKC-complex, NMDA-R, GAD or GLY-Rs. Ekizoglu and colleagues (Ekizoglu et al., 2014) reported the presence of (GLY-Rs), contactin-associated protein 2 (CASPR-2), NMDA-R, and VGKC-complex in 13.0% of patients with focal epilepsy of unknown cause and in the group with mesial temporal lobe epilepsy with hippocampal sclerosis.

Therefore, the role of autoimmunity has been proposed in the etiology of both new onset and chronic epilepsies. Furthermore, a relationship between autoimmune etiology and antiepileptic drug (AED) resistance has been reported, in which case immunomodulatory or immunosuppressive drugs may show some benefits (Sunwoo, 2016; McKnight et al., 2005; Quek et al., 2012; Dubey and Samudra, 2015).

In our study, we aimed (i) to analyse and confirm the presence of autoantibodies in focal epilepsy patients with unknown cause, (ii) to determine the clinical findings associated with these antibodies and (iii) to investigate the effectiveness of immunosuppression in controlling seizures in seropositive patients.

2. Patients and Methods

2.1. Participants

Between 2009 and 2010 94 patients were prospectively enrolled, had their antibodies tested and clinically followed. An additional 50 age- and gender-matched controls were also tested for antibodies at Epilepsy outpatient clinic of Istanbul University, Cerrahpasa School of Medicine, Department of Neurology. Only patients that gave their consent and were available for follow-up visits were recruited. Healthy controls were included only for assessment of the validity of antibody assays since false antibody seropositivity has been previously reported (Paterson et al., 2014).

Patients who were younger than 18 years at the time of blood sampling or had structural lesions in brain magnetic resonance imaging (MRI) such as tumor or dysplasia were excluded from the study. However, patients with focal or diffuse atrophy or nonspecific white matter hyperintensities were not excluded. In addition, none of the included patients had current findings or past medical history of any neurological conditions. Patients with systemic autoimmune disorders, febrile seizures or systemic infections were included if there was no direct temporal association between these medical conditions and the onset of seizures. Likewise, patients with mesial temporal lobe epilepsy with hippocampal sclerosis were not excluded since their seizure features and locations could not be explained by hippocampal sclerosis alone.

Seizures and syndromes were diagnosed according to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology 2014 (Fisher et al., 2014). After antibody detection patients were followed for 4 years for evaluation of treatment responses and seizure prognosis.

2.2. Clinical evaluation

All patients underwent detailed neurological examination. Demographical and clinical features including age at onset of seizures, duration of epilepsy, presence of antecedent immune related disorders, precipitating factors, findings of electroencephalography (EEG) (obtained on admission and during follow-up), neuroimaging findings in brain (MRI), AED usage, and response to treatment were recorded. All MRI studies were performed with 1.5 T scanners with thin coronal, sagittal and axial planes including T1, T2, and fluid-attenuated inversion recovery (FLAIR) images. Response to AED treatment was classified as a good or poor response. Good response was defined as being seizure-free or to have one seizure in the last year and poor response was defined as having two or more seizures in the last two months despite the use of adequate AEDs as previously accepted in the literature (Ekizoglu et al., 2014). Immunotherapy was administered in seropositive patients with poor response to AEDs after their informed consent. Other seropositive patients were only treated with AEDs.

This study was approved by the institutional ethical committee. Informed consent was obtained from all participants before blood sampling.

2.3. Autoantibody testing

The antibody testing was offered to every patient that met inclusion criteria and available for follow-up visits. Patients had visits scheduled according to their seizure frequency which ranged between 3 and 6 months. The visits included neurological examination, determination of seizure frequencies and investigation of EEG findings when possible. Seizure information was obtained with phone calls only in one case (case 12). None of the patients were lost to follow-up.

Plasma obtained from patients and from 50 healthy controls were frozen at -80°C and analysed for autoantibodies against VGKC-complex, LGI1, CASPR-2, NMDA-R, AMPA-R, GABAB-R, P/Q type VGCC and GAD with immunocytochemistry and radioimmunoassay technique as required.

NMDA-R, AMPA-R, LGI1, CASPR-2, and GABAB-R antibodies were detected by binding to HEK293 cells transfected with plasmids containing the NR1/NR2 subunits of the NMDA-R, GluR1/GluR2 subunits of the AMPA-R, LGI1, CASPR2, or GABAB-R subunit, respectively using a commercial kit (Euroimmun, Luebeck, Germany). Transfected cells were incubated with patients' sera (1:20) and the appropriate Alexa Fluor secondary antibody. The binding was scored visually on a range from 0 (negative) to 4 (very strong) as in previous studies (Irani et al., 2010). Only scores greater than one were accepted as positive to avoid nonspecific low positivity. For VGKC-complex (including LGI1, CASPR-2, contactin-1, Kv1 subunit proteins and other as yet unknown components), P/Q type VGCC and GAD antibodies, radioimmunoassay (RIA) kits using immunoprecipitation of ^{125}I -dendrotoxin (normal value < 100 pM), ^{125}I - ω -conotoxin (normal value < 100 pM) and ^{125}I -recombinant GAD (normal value < 10 U/ml) were used (RSR Limited, Cardiff, UK).

2.4. Statistical analysis

The presence of antibodies was compared between patients with epilepsy and healthy subjects. We dichotomized patient group according to the presence of antibodies as a seropositive group and a seronegative group. Demographical and clinical findings such as age at examination, gender, age at seizure onset, seizure frequency, risk

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