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ORIGINAL ARTICLE

Investigation of anti-neuronal antibodies in status epilepticus of unknown etiology: a prospective study

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Abstract There have been recent reports of antibody-mediated status epilepticus. The objective of our study was to investigate the prevalence of neuronal autoantibodies in patients with status epilepticus (SE) with unresolved etiology. The presence of neuronal autoantibodies was investigated prospectively in adult patients with SE who presented to our clinic between February 2012 and December 2013 with unresolved etiology. Clinical and electrophysiologic features of seropositive patients were recorded. Also, seronegative and seropositive patient groups were compared in terms of demographic and clinical features, treatment responses, and outcomes. Neuronal antibodies against *N*-methyl-D-aspartate receptor (NMDA-R) were positive in 2 patients, against glycine receptor (Gly-R) in 2 patients, and against gamma-aminobutyric acid-A receptor [GABA(A)R] in 1 patient, which constituted a total of 5 (22.7%) of 22 patients with SE with unidentified etiology. One of three patients with systemic tumors was positive for GABA(A)R antibody. Four patients had a short epilepsy duration, while one of the NMDA-R antibody-positive patients had chronic epilepsy and double cortex finding in MRI. There was no significant difference between seropositive and seronegative patient groups in terms of demographic and clinical features, treatment responses, and outcomes. Neuronal antibodies are found in a sizeable portion of de novo SE patients, who are potential candidates of autoimmune encephalitis. Alternatively, these antibodies may presumably also emerge in SE patients with a chronic epilepsy history as an epiphenomenon. Further research is required to make the distinction between these two different antibody formation mechanisms.

Keywords Status epilepticus · Autoantibodies · Glycine receptor · Gamma-aminobutyric acid-A receptor · *N*-methyl-D-aspartate receptor

Introduction

Recent identification of neuronal autoantibodies in patients with new-onset epilepsy has suggested an autoimmune origin for certain epileptic seizures [1–3]. Some of the distinguishing features of these patients were rapidly progressive short-term memory impairment, psychosis and other limbic encephalitis symptoms, inflammatory cerebrospinal fluid (CSF) findings, temporal lobe abnormalities in electroencephalography (EEG) and magnetic resonance imaging (MRI), and presence of anti-neuronal antibodies. Patients with limbic encephalitis have been shown to display antibodies against neuronal membrane antigens. These patients occasionally present with cancer and often respond well to immune therapy [4]. On the other hand, antibodies against neuronal membrane/synaptic antigens including voltage-gated potassium channel (VGKC) complex, glutamic acid decarboxylase (GAD), *N*-methyl-D-aspartate receptor (NMDA-R), and glycine receptor (Gly-R) have been demonstrated in 6–16% of patients with chronic epilepsy with seizures, as the primary or only clinical presentation, with no classic limbic encephalitis features, and no demonstrable inflammatory etiology [2, 5–9].

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Identification of these patients is important because they may plausibly be more refractory to anti-epileptic therapy and benefit from immunotherapy [2, 7, 9, 10].

Status epilepticus (SE) is one of the most important complications of epilepsy that lead to increased mortality and morbidity [11]. The recent International League Against Epilepsy (ILAE) classification defined SE as a condition that results either from the failure of the mechanisms responsible for seizure termination, or the initiation of mechanisms that lead to abnormally prolonged seizures (after time point T1), and can have long-term consequences (after time point T2) including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. T1 has been described as 5, 10, and 10–15 min, and T2 has been described as 30 min, >60 min, and "unknown" for tonic–clonic SE, focal SE with loss of consciousness, and absence SE, respectively [12].

There are many patients with SE in whom no clear etiology has been found despite satisfactory investigations [13, 14]. A few anecdotal case reports [15–17], a pediatric case series [18], and three retrospective studies [14, 19, 20] have highlighted the importance of autoimmunity in SE, but no prospective studies have investigated the presence and prevalence of neuronal autoantibodies in patients with SE.

The objective of this study was to demonstrate the presence of antibodies against well-characterized neuronal membrane and/or synaptic autoantigens in patients who presented to our tertiary university hospital clinic and were diagnosed as having SE with unidentified etiology, and thus to investigate the role of autoimmunity in the etiology of SE.

Methods

Participants

This was a prospective cohort of 59 adult patients who were diagnosed as having SE between February 2012 and December 2013; a total of 37 patients with an identified etiology were excluded. The excluded patients had acute cerebrovascular diseases ($n = 6$), brain tumors ($n = 10$), abrupt discontinuation of anti-epileptic drugs ($n = 6$), genetic epilepsy syndromes with frequent SE ($n = 2$), head trauma ($n = 2$), anoxia ($n = 1$), central nervous system (CNS) vasculitis ($n = 1$), CNS infection ($n = 1$), and marked metabolic impairment and drug-substance intoxication ($n = 8$); a total of 22 patients with SE of unidentified etiology were included in the final analysis.

Clinical, demographic, imaging, and other laboratory findings of the patients were recorded. As the control groups, 30 age- and sex-matched healthy volunteers, and 50 patients with relapsing-remitting multiple sclerosis (RRMS) were also enrolled. The study was approved by the Institutional Ethics Committee of Istanbul University Istanbul Medical Faculty (12/1229). Informed consents were obtained from all patients or their legal guardians and controls, following provision of detailed information on the study examinations and tests.

Convulsive SE (CSE) was defined as seizures lasting longer than 5 min or two seizures without achievement of consciousness in between [21], and non-convulsive SE was defined as altered consciousness or behavior compared with normal lasting at least 30 min with one or more epileptiform patterns as defined in the review of Kaplan, and without accompanying convulsive movements [22]. Epilepsia partialis continua (EPC) was defined as focal clonic seizures localized to a part of the body lasting at least 30 min, often with preserved consciousness, although altered consciousness might also accompany [23].

Surface electrodes were placed using the international 10–20 system to obtain a 21-channel electroencephalograph (EEG) in the laboratory or at the bed side. Patients' consciousness, response to activation methods, and presence of seizures were recorded from technician notes or video records.

A stepwise treatment protocol was administered to patients in line with the current guidelines [24]; intravenous benzodiazepine was administered as first-line therapy when there were no contraindications, followed by phenytoin therapy. One or both of levetiracetam or valproate were loaded intravenously in refractory cases. Coma induction was performed in further refractory patients under intensive care unit conditions.

Antibody testing

Serum samples were obtained during SE or in the 24 h following termination of SE. Sera were stored at −80 °C until assayed and were investigated for serum antibodies against VGKC-complex antigens, contactin-associated protein-like 2 (CASPR-2), leucine-rich glioma inactivated 1 (LGI1), GAD, NMDA-R, GLY-R, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), and type A and B gamma-aminobutyric acid receptors ($GABA_AR$, $GABA_BR$). Antibodies to neuronal membrane antigens were investigated using a commercial kit (Euroimmun, Luebeck, Germany) that contained HEK293 cells transfected with plasmids containing NR1/NR2 subunits of NMDA-R, and GluR1/GluR2 subunits of AMPA-R, CASPR2, LGI1, and $GABA_BR$.

Positive results were confirmed using a home-made assay with live HEK293 cells transfected with relevant plasmids. Due to the absence of a commercial kit,

antibodies to the α1 subunit of the GLY-R or α1/γ2 subunits of $GABA_AR$ were only detected using live HEK293 cells. Transfected cells were incubated with the patients' sera (1:20) and the appropriate Alexa Fluor secondary antibody, as described in previous literature [7, 25–27]. All positive results were repeated using an IgG-specific secondary antibody (Alexa Fluor 488-anti-IgG Fc; 1:500, Invitrogen, Carlsbad, CA, USA) in order to avoid detection of IgM antibodies [28]. Antibody-positive sera were re-tested for antibodies with serial dilutions of two-fold from 1:20 to 1:640. Detection of antibodies to uncharacterized VGKC-complex antigens (normal values <50 pM) or GAD (normal values <10 U/mL) were performed using a radioimmunoassay (RIA; RSR, Cardiff, UK). Hu, Yo, CV2, Ri, Ma2, and amphiphysin antibodies were investigated using a commercial immunoblot kit (Euroimmun) in cases with an accompanying systemic cancer.

Statistical analysis

Descriptive statistics were applied, and the two groups of patients with and without serum antibodies were compared using the Chi-square test, Fisher's exact test, and independent samples t test, where appropriate. Statistical Package for Social Sciences version 18 (SPSS Inc, Chicago, IL, USA) was used and the significance level was set at $p < 0.05$.

Results

The 22 patients included in the study comprised 18 females (81%) and 4 males (19%). The patients' age ranged between 17 and 90 years (mean: 48.4 ± 23 years). SE subtypes were CSE in 12 patients, EPC in 4 patients, and NCSE in 6 patients. Nine patients had no history of epilepsy (de novo SE). Neuronal antibodies against NMDA-R were positive in 2 patients, Gly-R in 2 patients, and GABA(A)R in 1 patient, constituting a total of 5 patients (22.7%). Antibody-positive sera remained seropositive in all tested serum dilutions. No antibodies were identified against CASPR-2, LGI1, uncharacterized VGKC-complex antigens, or AMPA-R or $GABA_BR$. The investigated autoantibodies were absent in the healthy controls or patients with RRMS. The medical history, clinical and laboratory data, drug history, and clinical course of seropositive patients are shown in Table 1.

Four patients with genetic epilepsy syndrome were taking appropriate medications and no other provocative factors could be found. Two patients with hippocampal sclerosis progressed into convulsive SE, which is rare [29]. Two study patients were diagnosed as having multiple sclerosis (MS). Although SE is seen more commonly than expected in patients with MS, it is still rare in MS, and patients with SE and MS are accepted as having unresolved etiology [30].

One patient who was diagnosed as having double cortex had had refractory focal epilepsy since the age of 19 years and was included in the study upon the development of SE for the first time in the absence of any provocative factors, and NMDA-R antibodies were detected in this patient. One of the seronegative patients had Crohn's disease and another seronegative patient was diagnosed as having encephalitis with no identifiable viral pathogens and unresolved etiology.

Three patients had systemic malignancies. Two seronegative patients had colon cancer and cholangiocarcinoma. One anti-GABA(A)R antibody-positive patient had cholangiocarcinoma. All three patients had normal CSF and cranial MRI examinations, and all were negative for Hu, Yo, CV2, Ri, Ma2, and amphiphysin antibodies.

Seronegative and seropositive patients were compared in terms of age, duration of epilepsy, sex, treatment response, history of febrile convulsion, presence of psychiatric diseases, any previous diagnosis of epilepsy, mortality, MR abnormalities, and SE subtype, and no significant difference was found between the groups (Table 2).

Immunotherapy was not performed in patient 1, 2, and 4 who died because antibody testing took several months. Patient 3 became seizure-free with anti-epileptic drugs and did not need immunotherapy. Patient 5 refused immunotherapy.

Discussion

The results of our prospective study demonstrated that neuronal autoantibodies were detected in SE in 5 (22.7%) out of 22 patients with de novo SE or epilepsy with unresolved etiology, which indicates the importance of the search for neuronal autoantibodies in SE with unresolved etiology. Concurrence of SE and antibodies against NMDA-R, GAD, and VGKC-complex antigens has often been reported in adult [19, 31] and pediatric [18, 32] patients with a clinical picture of encephalitis. In our study, seropositive patients did not have typical cranial MRI findings of limbic encephalitis and inflammatory CSF findings. Notably, our seropositive patients except patient 5 had a short disease duration thus ruling out blood–brain barrier breach and subsequent antibody formation as an epiphenomenon due to chronic epileptic activity. Thus, it is tempting to speculate that our seropositive patients presented with autoimmune encephalitis without full-scale limbic encephalitis findings and only with isolated seizures and SE (and cognitive impairment in two).

Table 1 The clinical and EEG characteristics, laboratory findings, treatment responses, and outcomes in the antibody-positive patients

No	Sex, age	Presentation	Epilepsy history and treatment	Medical history	Examination	Laboratory findings	MRI	EEG	Treatment of SE	Outcome	Antibody
1	F, 77	Blurred consciousness of unknown cause since 1 week	De novo SE (NCSE)	Cholangiocarcinoma and adrenal metastasis	Normal except for confusion	Normal CSF examination Paraneoplastic[a] antibodies are negative	Normal cranial MRI with contrast	Generalized sharp and sharp slow waves as double- or triple-series, intermittently continuous on HAAs (NCSE)	20 mg BZD 1400 mg PHT,2000 mg LEV	Exitus due to deterioration of overall condition at 15 days	Anti-GABA (A)R antibodies (1/640)[b]
2	F, 67	GTCS and continuous facial twitches afterwards	De novo SE (CSE); Ceftriaxone was initiated for pneumonia	MS	Comatose	Normal blood and CSF examinations Paraneoplastic antibodies[a]were negative	Periventricular MS plaques	Generalized periodical epileptiform discharges (ictal)	20 mg BZD, 2000 mg LEV, 200 mg TPM, coma induction (super-refractory SE)	SE ended after 1 week, and patient responded with eye opening to painful stimuli. Deceased due to septic shock and pneumonia after 4 months of intensive care unit stay	Anti-Gly-R antibodies (1/640)
3	M, 17	GTCSs. First SE	Diagnosed with epilepsy 1.5 months ago. LEV, VPA, LTG	Nonspecific	Mild mental retardation	Normal blood and CSF examinations	Normal MRI	Generalized paroxysmal sharp and slow waves and postictal slowing	2000 mg LEV	SE was stopped. Follow-up EEGs were normal. No seizures since 2 years with LEV and ZNS	Anti-Gly-R antibodies (1/640)
4	F, 42	Right focal clonic and sGTCSs	Focal refractory epilepsy with unidentified cause since 1 year. VPA, LEV, CZM	Hypertension Cystitis: piperacillin tazobactam	Right hemiparesis, confusion Fever 39 Cognitive impairment	CUA: +++ bacteria, 312/HPF leukocytes	Left hippocampal and left hemispheric atrophy	Continuous sharp waves with wide base and continuous irregular slow waves at theta frequency on left HAA (interictal)	8 mg BZD, 2000 mg PHT, 1500 mg LEV 500 mg VPA, 2 mg CZM	SE was stopped, in the follow-up patient was deceased during an episode of multiple AED refractory SE	Anti-NMDA-R antibodies (1/640)
5	F, 25	Frequent focal seizures with fear aura and confusion. First SE	FC (+). Experiences generalized convulsions and frequent complex partial seizures at every 2–3 months since 6 years old. CZP	Psychotic complaints	Confusion	Normal blood examination	Double cortex appearance	Isolated and once in the form of 12-sec-long series generalized spikes and sharp waves on HAF and right hemisphere. TA: 5–6 Hz (postictal)	20 mg BZD, 3000 mg LEV	SE was stopped. 2 more SE,frequent focal seizures with LEV, LCM CZP	Anti-NMDA-R antibodies (1/640)

CUA complete urine analysis, *MRI* magnetic resonance imaging, HAA: hemisphere anterior areas, *GTCS* generalize tonic–clonic seizure, *sGTCS* secondary generalized tonic–clonic seizure, *SE* status epilepticus, *CSE* convulsive status epilepticus, *NCSE* non-convulsive status epilepticus, *AED* anti-epileptic drug, *CSF* cerebrospinal fluid, *FC* febrile convulsion, *LEV* levetiracetam, *LCM* lacosamide, *CZP* carbamazepine, *BZD* benzodiazepine, *VPA* valproic acid, *TPM* topiramate, *PHT* phenytoin, *CZM* clonazepam, *LTG* lamotrigine, *ZNS* zonisamide

[a] Investigated paraneoplastic antibodies against intracellular antigens are Hu, Yo, CV2, Ri, Ma2, and amphiphysin

[b] Numbers in brackets indicate endpoint dilutions

Table 2 Comparison of the clinical features of patients with and without autoantibodies

	Seropositive patients $N = 5$ (%)	Seronegative patients $N = 17$ (%)	p values
Sex (female/male)	4/1 (80/20)	14/3 (82.4/17.6)	NS
Age at serum sampling (years ± SD)	46 ± 26	49 ± 23	NS
Epilepsy duration (years ± SD)	4 ± 8	9 ± 13	NS
Poor AED response	4 (80)	11 (64.7)	NS
Febrile seizures	1 (20)	4 (23.5)	NS
Psychiatric disorders	1 (20)	3 (17.6)	NS
Previous epilepsy	3 (60)	10 (58.8)	NS
Mortality	3 (60)	7 (41.2)	NS
MRI abnormalities	3 (60)	8 (47.1)	NS
SE type			
CSE	3 (60)	9 (52.9)	NS
NCSE	2 (40)	4 (23.5)	NS
EPC	0 (0)	4 (23.5)	NS

AED anti-epileptic drug, *SE* status epilepticus, *CSE* convulsive status epilepticus, *NCSE* non-convulsive status epilepticus, *EPC* epilepsia partialis continua, *SD* standard deviation, *NS* not significant

On the other hand, detection of NMDA-R antibodies in patient 5 with the double cortex finding and chronic epilepsy suggest that anti-neuronal antibodies might also emerge as a bystander effect of prolonged seizures in some status epilepticus or chronic epilepsy patients and thus antibody positivity should be evaluated with caution. Clinical findings do not appear to assist the discrimination of causative and resultant antibodies in patients presenting with seizures only and therefore additional experimental research is presumably required for this distinction.

In a previous study, 6% ($n = 33$) of 570 consecutive SE episodes was inflammatory (including infectious and autoimmune). Two of the patients had antibodies against NMDA-R and one had antibodies against ANNA-2. Inflammatory SE episodes were more common in younger patients and higher refractoriness to treatment in this group had no effect on outcomes compared with non-inflammatory SE episodes. Also, autoimmune SE episodes were shown to have better outcomes in survivors than infectious SE episodes [20]. In another study, in 52% of 130 cases with new-onset refractory SE, etiology could not be revealed while autoimmune (19%) and paraneoplastic (18%) encephalitis were the most common identified etiologies. The most commonly found antibodies were against NMDA-R, and VGKC-complex antigens. There were no differences between cryptogenic patients and patients with autoimmune and paraneoplastic encephalitis in terms of clinical presentation, EEG, imaging, CSF findings and outcome which suggested that some of the cryptogenic cases could have autoimmune encephalitis with antibodies yet to be identified [14]. Also in this study, we identified no differences between seronegative and seropositive patients with SE; however, the small size of our patient population should be noted.

Antibodies against Gly-R were first identified in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) [33]. In a comprehensive prospective study, 52 patients with antibodies against Gly-R were reported, most of whom were diagnosed as having PERM, while five had limbic encephalitis or epileptic encephalopathy. Most of the patients were shown to respond well to immunotherapy [34]. A case of a young child with focal status epilepticus and progressive dyskinesia in whom antibodies against Gly-R was reported recently [35]. We identified Gly-R antibody in patient 2 who was diagnosed as having de novo super-refractory SE, and patient 3 who had generalized epilepsy with a good clinical course, and found the prevalence as 9.5% in our SE cohort. The patients did not have homogeneous clinical pictures. As mentioned before, our patients who presented with SE were different from the patients in literature in terms of not having inflammatory CSF changes and cranial MRI findings.

GABA(A)Rs are ionotropic receptors on the cell membrane that regulate rapid inhibitory neurotransmission [36]. High titers of antibodies against these receptors have been demonstrated in serum and CSF of patients with encephalitis who presented with refractory seizures and SE with pleocytosis, elevated CSF protein levels, and abnormal MRI findings in recent reports. One of these patients was diagnosed as having lymphoma [37]. Non-Hodgkin lymphoma recurrence, CSF pleocytosis, and oligoclonal bands, as well as temporal hyperintensity in MRI have been determined in another case [27]. These studies concluded that GABA(A)R antibody-positive patients benefit from immunotherapy.

The etiology has often been associated with novel or existing neoplastic involvement of the central nervous

system in patients with cancer and NCSE [38]. However, patients with cancer who have NCSE and no identifiable cranial involvement have also been reported [39, 40]. Our patient stands out as the first reported GABA(A)R antibody-positive patient with cancer and NCSE and no neoplastic involvement of the central nervous system, and highlights the importance of the search for this antibody. This patient could have been considered to have a paraneoplastic syndrome (PNS) but isolated SE is not a classical PNS and GABA(A)R antibody is not a well-defined paraneoplastic antibody. Thus findings of this patient do not strictly fulfill the diagnostic criteria for PNS [41]. However, GABA(A)R antibody-positive autoimmune encephalitis patients might present with only seizures and no other neurological findings [37] and thus it is probable that GABA(A)R antibodies have a causal role in this patient. It should also be noted that main epitope targets in GABA(A)R encephalitis have been determined as α1 and β3 subunits of the receptor [42]. Since we did not investigate β3 subunit antibodies, there might be additional patients in our cohort with GABA(A)R antibodies.

It can be argued that MS might be involved in the generation of SE. SE has been reported to remain refractory to conventional anti-epileptic drugs, and improve with treatment of MS relapse [43]. Although epilepsy has been reported to occur more commonly in patients with MS, its prevalence has been calculated as 1.5% in adult onset MS patients in a Turkey-based study, and is comparable to the 1.17% overall epilepsy prevalence in Turkey [44]. Poser and Brinar determined that evidence for a direct relationship between a specific lesion and seizures is sparse, and the fact that most patients have generalized seizures is incompatible with focality of MS; and seizures remain to be rare in MS patients despite the abundance of cortical and subcortical lesions [45]. Our patient had the diagnosis of MS for a very long time without follow-up. She presented with primary generalized super-refractory SE which was her first seizure, which makes her clinical features extremely difficult to relate to one another. Furthermore, she had no new lesions in cranial MRI. Thus this patient was also considered as an epilepsy patient with unresolved etiology. We reported this patient previously [43] and speculated that the underlying mechanism may have been the exposure of the immune system to CNS antibodies due to a leakage in the blood–brain barrier and synthesis of epileptogenic autoantibodies, including Gly-R, as described in previous studies [44].

One limitation of this study is that immunotherapy could not be given to some patients. Patients 1, 2, and 4 died before antibody testing resulted, patient 3 became seizure-free with anti-epileptic drugs, and patient 5 refused immunotherapy. Other limitations are that we did not repeat measurements of serum antibodies and CSF samples could not be investigated due to a lack of consent from our regional review board. The most important strength of our study was its prospective design, and relatively high prevalence of neuronal autoantibody positivity, which suggests that patients with SE of unknown etiology should be investigated for a possible autoimmune etiology. On the other hand, no difference could be detected between seropositive and seronegative patients with regard to clinical features, treatment responses, and outcomes, and thus we could not identify any clinical clues for the presence of anti-neuronal antibodies. This could be due to the small size of our patient population and lack of repeated antibody measurements. Also, it remains controversial whether neuronal autoantibodies are pathogenic in themselves, or they are merely markers of other direct pathogenic processes. Future studies are needed to draw further conclusions.

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Compliance with ethical standards

Conflict of interest The authors reported no conflict of interest related to this article.

Ethical standards The study was approved by the Institutional Ethics Committee of Istanbul University Istanbul Medical Faculty (12/1229).

Informed consent Informed consents were obtained from all patients or their legal guardians and controls, following provision of detailed information on the study examinations and tests.

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