J Neurol (2016) 263:455–466
DOI 10.1007/s00415-015-8002-2

ORIGINAL COMMUNICATION

Neuronal autoantibodies in epilepsy patients with peri-ictal autonomic findings

Leyla Baysal-Kirac[1] · Erdem Tuzun[2] · Ece Erdag[2] · Canan Ulusoy[2] · Ebru Nur Vanli-Yavuz[1] · Esme Ekizoglu[1] · Sian Peach[3] · Mine Sezgin[1] · Nerses Bebek[1] · Candan Gurses[1] · Aysen Gokyigit[1] · Angela Vincent[3] · Betul Baykan[1]

Received: 17 October 2015 / Revised: 12 December 2015 / Accepted: 16 December 2015 / Published online: 2 January 2016

Abstract Autonomic dysfunction has frequently been reported in autoimmune encephalitis associated with seizures and there is growing evidence that epilepsy patients may display neuronal autoantibodies (NAAb). The aim of this study was to investigate the frequency of NAAb in epilepsy patients with peri-ictal autonomic findings. Fifty-eight patients (37 women/21 men; average age of 34.2 ± 9.9 years and epilepsy duration of 19.1 ± 9.6 years) who had at least one video-EEG recorded focal or secondary generalized seizure with clear-cut documented peri-ictal autonomic findings, or consistently reported seizures with autonomic semiology, were included. NAAb were tested by RIA or cell based assays. NAAb were present in 17 of 58 (29.3 %) patients. Among seropositive patients, antibodies were directed against *N*-methyl-D-aspartate receptor (NMDAR) in 5 (29 %), contactin-associated protein-like 2 (CASPR2) in 5 (29 %), uncharacterized voltage gated potassium channel (VGKC)-complex antigens in 3 (18 %), glutamic acid decarboxylase (GAD) in 2 (12 %), glycine receptor (GLYR) in one (6 %) and type A gamma aminobutyric acid receptor ($GABA_AR$) in one patient (6 %). Peri-ictal gastrointestinal manifestations, piloerection, ictal fever, urinary urge, and cough occurred more commonly in the seropositive group. The prevalences of psychotic attacks and status epilepticus were significantly increased in the seropositive group. Seropositivity prevalence in our patient group with peri-ictal autonomic findings is higher than other previously reported epilepsy cohorts. In our study, ictal fever-VGKC-complex antibody and pilomotor seizure-$GABA_AR$ antibody associations were documented for the first time. Chronic epilepsy patients with peri-ictal autonomic semiology, history of status epilepticus and psychotic disorder may benefit from autoantibody screening.

Keywords Autoimmune epilepsy · Limbic encephalitis · Autonomic seizure semiology · NMDAR · VGKC Ab

Introduction

The etiology of epilepsy is currently unknown but is presumed to be multifactorial with both genetic and environmental factors [1]. Recently, autoantibodies to specific neuronal targets including the voltage gated potassium channel complex (VGKC-complex), *N*-methyl-D-aspartate receptor (NMDAR), glutamic acid decarboxylase (GAD) and glycine receptor (GLYR) have been identified as possible causes of epilepsy in limbic encephalitis and idiopathic cases [2–13]. Search for autoimmunity is now recommended in the presence of antiepileptic drug (AED) resistance, personal or family history of autoimmunity, recent or past neoplasia, nonspecific white matter changes on magnetic resonance imaging (MRI) or psychosis [4, 6, 8]. Identification of specific autoantibodies and subsequent immunotherapy appear to result in substantially improved seizure control in some patients [4, 9].

Autonomic instability has frequently been reported in antibody-associated forms of encephalitis suggesting that autonomic structures of the nervous system may be among the targets of these autoantibodies. Pilomotor seizures

✉ Leyla Baysal-Kirac
baysalleyla@gmail.com

[1] Department of Neurology and Clinical Neurophysiology, Istanbul Faculty of Medicine, Istanbul University, 34093 Capa, Fatih, Istanbul, Turkey

[2] Department of Neuroscience, Institute of Experimental Medical Research, Istanbul University, Istanbul, Turkey

[3] Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, UK

(goose bumps) were identified in autoimmune limbic encephalitis [4, 12, 13] and dysautonomic features such as central hypoventilation, hyperhidrosis, pyrexia and tachy/bradycardia appear frequently during the course of NMDAR-antibody encephalitis and may accompany seizures [10, 11]. Likewise, in Morvan's syndrome which is associated with neuromyotonia, autonomic disturbances, sleep and cognitive disorders VGKC-complex antibodies are very frequent [14, 15]. However, the frequency of neuronal autoantibodies (NAAb) in epilepsy patients with peri-ictal autonomic symptoms has so far not been not systematically documented.

In this study, we screened sera from consecutive epilepsy patients with peri-ictal autonomic findings and investigated the clinical and EEG features of patients with NAAb. Our aim was to determine the incidence of serum NAAb in patients with autonomic seizure semiology, and possible relation of autoimmunity and its markers in patients with chronic epilepsy having autonomic seizure components.

Methods

Study population

Consecutive epilepsy patients who described reliable autonomic auras and had at least one video-EEG-polygraphically recorded focal or secondarily generalized seizure with clear-cut documented peri-ictal autonomic findings ($n = 43$) were enrolled in the study. Video-polygraphically recorded peri-ictal autonomic features with cardiovascular (tachycardia, bradycardia, cardiac arrhythmias), respiratory (cough, hyperventilation, apnea), gastrointestinal (epigastric aura, nausea, vomiting, retching, spitting, perictal water drinking), thermoregulatory (fever), vasomotor, pilomotor and secretory (piloerection or goosebumps, flushing, hypersalivation), genital and urinary manifestations (genital automatisms, urinary urge, urinary incontinence) were systematically monitored. The peri-ictal period was defined as extending from the beginning of the aura when present, to 3 min after clinic/electrographic seizure offset. Additionally, 15 epilepsy patients, whose autonomic seizures had not been recorded by video-EEG but consistently, displayed seizures with autonomic semiology that were witnessed, were also included.

We included 58 consecutive patients (female/male 37/21; mean age 34.2 ± 9.9 years, range 15–57 years; mean duration of epilepsy 19.1 ± 9.6 years, range 3–45 years) who were followed up by Istanbul Faculty of Medicine, Epilepsy Center (EPIMER) between the years 2011 and 2014. Forty-nine of 58 patients had been admitted to the epilepsy monitoring unit for presurgical evaluation or differential diagnosis of epilepsy. Remaining 9 patients were followed up at epilepsy outpatient clinic, regularly.

The main etiologies of the patients were mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) in 34 (59 %); focal epilepsy of unknown cause (FEoUC) in 15 (26 %); cortical dysplasia in four (7 %); multiple sclerosis, Rasmussen encephalitis or systemic lupus erythematosus (SLE) in three (5 %), neoplasm in one (2 %); and hypoxic ischemic brain injury in one (2 %) patient. Thus, only three patients were already known to have an immune-mediated disease. Fifty-two of 58 patients (90 %) had AED-resistance. Epilepsy surgery had been performed on 20 patients. Seventeen of them had a good surgical outcome (Engel class 1) with at least 1 year follow up.

Our primary aim was to screen the frequency of NAAb in chronic epilepsy patients without additional autoimmune encephalitis findings. Hence we did not include the patients with acute/subacute onset of possible autoimmune encephalitis according to the suggested criteria by Zuliani et al. [16]. Therefore, patients with a history of acute/subacute onset of epilepsy and other findings related to limbic system or evidence of MRI and cerebrospinal fluid abnormalities that are commonly observed in limbic encephalitis or any other antibody mediated neuroinflammatory disease were specifically excluded. The clinical and laboratory characteristics of patients with autoimmune encephalitis who were followed in our clinic during the same years were mentioned in a recent report [17]. As the control groups, age and gender-matched 30 healthy volunteers and 50 relapsing remitting multiple sclerosis (RRMS) patients were also enrolled. The study was approved by the ethics committee. Informed consent was obtained from all participants before blood sampling.

Study design

Information regarding demographic data, neurological symptoms, age at onset, epilepsy duration, epilepsy etiology, medical and family history, history of autoimmune disorders, AEDs at the time of serum sampling, response to treatment and detailed EEG and neuroimaging data were collected retrospectively from the files. Serum samples for the purpose of antibody analysis were collected during routine outpatient interviews.

Patients were evaluated with detailed clinical examination, seizure history and video EEG monitoring with scalp electrodes. The patients had 32-channel, non-invasive EEG monitoring with 10–20 system electrodes and ECG electrodes. All underwent high resolution MRI examinations with 1.5 T scanners with thin coronal, sagittal and axial planes including T1, T2, and fluid-attenuated inversion recovery (FLAIR) images according to a standard epilepsy protocol and evaluated by an experienced neuroradiology

team. Interictal fluordeoxyglucose positron emission tomography (FDG-PET) were performed in selected patients ($n = 37$).

Seizures and syndromes were diagnosed according to the revised terminology, and concepts for organization of seizures and epilepsies of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology, and their semiological findings and auras were classified according to Glossary of the ILAE Task Force on Classification and Terminology [18, 19]. The syndrome diagnosis was supported by at least two congruent results from EEG and imaging studies (MRI and PET). In patients with nonspecific MRI and functional imaging findings, the lateralization of epileptic zone was based only on EEG and seizure semiology. All patients were discussed in a multidisciplinary case management conference based on results of EEG-video monitoring and imaging findings.

AED-resistant epilepsy was defined according to the ILAE commission proposal; failure of adequate trials of two tolerated appropriately chosen and used AED drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [20]. All patients during preoperative investigations were examined by the same psychiatry team experienced in the management of epilepsy patients. Additionally, patients were sent to the same team if the neurologist observed or patients complained from some psychiatric problems during regular visits. Psychiatric diagnoses were classified according to the DSM IV manual.

Two authors re-analyzed and investigated all seizures for the reliability of the autonomic features, carefully (L.B.K and B.B). Only those signs on which both observers agreed were included in further analysis.

Autoantibody testing

All patients and controls were tested for serum antibodies to VGKC-complex antigens, contactin-associated protein-like 2 (CASPR2), leucine-rich glioma inactivated 1 (LGI1), GAD, NMDAR, GLYR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and type A and B gamma aminobutyric acid receptors ($GABA_AR$, $GABA_BR$). Sera were kept at −80 °C until assayed. Ion channel antibodies were detected by a commercial kit (Euroimmun, Luebeck, Germany) containing HEK293 cells transfected with plasmids containing the NR1/NR2 subunits of the NMDAR, GluR1/GluR2 subunits of the AMPAR, CASPR2, LGI1 and $GABA_BR$. Positive results were confirmed by using a home-made assay utilizing live HEK293 cells transfected with relevant plasmids. Due to absence of a commercial kit, antibodies to the α1 subunit of the GLYR or α1/γ2 subunits of the $GABA_AR$ were only detected by live HEK293 cells. Transfected cells were incubated with patients' sera (1:20) and the appropriate Alexa Fluor secondary antibody, as described earlier [6, 10, 21, 22]. All positive results were repeated using an IgG-specific secondary antibody (Alexa Fluor 488-anti-IgG Fc; 1:500, Invitrogen, Carlsbad, CA) to avoid detection of IgM antibodies [23]. The binding was scored visually on a range from 0 (negative) to 4 (very strong), as previously described [10, 21, 23, 24]. Only scores greater than 1 were accepted as positive to avoid nonspecific low positivity [24]. Detection of antibodies to the VGKC-complex (normal values <50 pM) or GAD (normal values <10 U/ml) were performed by radioimmunoassay (RIA; RSR, Cardiff, UK).

In addition, an indirect immunohistochemistry test was performed to determine serum samples with neuropil (neuronal axons and dendrites located in hippocampal molecular layer) antibodies, the presence of which are suggestive of neuronal surface antibody positivity. Whole rat brain was first treated with 4 % paraformaldehyde overnight at 4 °C, then immersed in 40 % sucrose overnight at 4 °C, and then snap frozen in liquid nitrogen. Seven micrometer-thick frozen sections were serially incubated with 0.3 % H_2O_2 for 20 min, 10 % goat serum for 1 h and serum samples (1:200) overnight at 4 °C. They were then incubated with biotinylated goat anti-human IgG (1:2000, Vector Laboratories, Burlingame, CA), and the immunoreactivity developed by serial incubation with avidin–biotin peroxidase (Vector Laboratories) for 1 h and diaminobenzidine [11].

Statistical analysis

Descriptive statistics were applied, and the two groups of patients with and without serum antibodies were compared with Chi-square test, Fisher's exact test, and independent samples t test, where appropriate. SPSS 15 software (SPSS Inc, Chicago, IL, USA) was used and the significance level was set at $p < 0.05$.

Results

Clinical characteristics of seropositive patients

Overall, the investigated autoantibodies were present in 17 (mean age 33.3 ± 10.6 years, female/male 9/8) of 58 patients (29.3 %) compared with none of the healthy controls or RRMS patients tested. These antibodies were directed against NMDAR ($n = 5$, 29 %), CASPR2 ($n = 5$, 29 %), uncharacterized VGKC-complex antigens ($n = 3$, 18 %), GAD ($n = 2$, 12 %), GLYR ($n = 1$, 6 %) and $GABA_AR$ ($n = 1$, 6 %) (Table 1). Fourteen of 17 seropositive epilepsy patients showed strong hippocampal

neuropil staining, whereas none of the seronegative epilepsy patients and controls showed neuropil staining. Patients with well-characterized NAAb and/or neuropil staining on immunohistochemistry were accepted as antibody positive. None of the CASPR2 antibody positive patients had VGKC-complex antibodies and vice versa. One of the GAD-antibody positive patients had type 1 diabetes mellitus (DM). Clinical and laboratory features of antibody-positive patients are presented in Tables 1 and 2.

The following peri-ictal autonomic findings were observed in the seropositive patients: gastrointestinal findings in 8 (47 %), tachycardia in 7 (41 %), cough in 3 (18 %), pilomotor manifestations in 2 (12 %), fever in 2 (12 %), hypersalivation in 2 (12 %), urination in 2 (12 %), bradycardia and hypoventilation, flushing, spitting, genital automatisms, and peri-ictal water drinking in one (6 %) patient, each.

Two patients with bilateral MTLE-HS who were seropositive for VGKC-complex antibodies suffered from seizures accompanied by documented episodes of early and remitting post-ictal fever. One of them (patient 6) was followed in the epilepsy monitoring unit for 4 days. Just after the seizures, he experienced fever at about 37.9–38.2 °C for 12 h which resolved spontaneously. Clinical examination and laboratory work up (C-reactive protein, leukocyte count, urine-analysis, chest x-ray) clearly ruled out an infection. In the other patient (patient 7) EEG monitoring performed over 5 days did not capture any seizures. However, he had consistently suffered from many witnessed and documented postictal fever attacks which lasted for about 24 h without any infection.

Pure autonomic seizures were seen in only two of the seropositive and five of the seronegative patients. In six of the patients other auras including affective, cephalic, auditory, and somatosensory auras had accompanied autonomic auras.

Table 3 comparatively outlines clinical and laboratory features of the groups with and without antibodies. The prevalence of psychotic attacks and status epilepticus were significantly more frequent in the seropositive group ($p = 0.01$ for both). Four out of 17 patients had interictal and one had post-ictal psychosis (Table 1). Peri-ictal gastrointestinal manifestations, piloerection, fever, urinary urge and cough occurred more commonly in the seropositive group without reaching statistical significance. There was no relationship between seropositivity and other clinical phenomena including epilepsy duration, AED resistance, history of febrile seizures, epilepsy etiology (MTLE-HS, FEoUC, other symptomatic causes) and coexisting autoimmune diseases. Among the 43 patients with symptomatic epilepsy and 15 patients with FEoUC, the prevalence of seropositivity (23 and 46 %, respectively) was higher in the non-symptomatic group without reaching statistical significance.

In the seropositive group, 10 patients (59 %) had a structural cause of epilepsy: 8 MTLE-HS, one focal cortical dysplasia and one hypoxic-ischemic brain injury secondary to birth trauma. The remaining 7 patients (41 %) had FEoUC. In the MTLE-HS group, there were VGKC-complex antibodies in three, CASPR2 antibodies in three, NMDAR antibodies in one and $GABA_AR$ antibodies in one patient. In the FeoUC group there were NMDAR antibodies in four, CASPR2 antibodies in one, GAD antibodies in one and GLYR antibodies in one patient. Among the seropositive group, 14 patients (76 %) had poor response to AED. In 5 patients selective amygdalohippocampectomy or anterior temporal lobectomy and in one patient vagal nerve stimulation (VNS) had been performed at least 1 year prior to the serum sampling. Three out of 5 operated seropositive patients had seizure freedom with Engel I outcome after the surgery, whereas another one had a remarkable seizure frequency reduction, but achieved no seizure freedom (Engel IIa). The last one had no improvement after the epilepsy surgery (Engel IV). The neuropathological examination of surgical specimens of these patients showed findings compatible with the pathological diagnosis of hippocampal sclerosis and did not show any inflammatory changes. One patient (patient 8, VGKC-complex antibody positive) with MTLE–HS, who was a candidate for epilepsy surgery but rejected the operation, had spontaneous remission and became seizure free after enduring AED drug-resistant seizures for 40 years, intriguingly. In their last follow up, three patients had seizure frequency reduction after changes in AED treatments. Immunotherapy and invasive EEG monitoring were planned for remaining patients who did not respond to AEDs. One patient with GAD antibody (patient 16) and one with CASPR2 antibody (patient 13) received intravenous methylprednisolone treatments (1000 mg/day on five consecutive days) which were followed by 1 day/-month pulses for the following 2 months. No seizure reduction was observed after 3 months of initial therapy for these patients.

In the seropositive group interictal EEGs showed background theta slowing in 3 patients (17.6 %). Interictal sharp waves and spikes were seen in 15 out of 17 patients (88 %) which were unilateral in 7 (47 %) and bilateral in 8 (53 %). Two patients had temporal intermittent rhythmic delta activity (TIRDA) and one had frontal intermittent rhythmic delta activity (FIRDA) in the EEG. Patterns such as periodic lateralized epileptiform discharges (PLEDs), generalized periodic discharges (GPDs) and extreme delta-brush were not seen in the group. Focal slowing was present in 15 of the patients (88 %), most common regions affected were temporal and frontotemporal areas.

Table 1 Clinical characteristics of seropositive patients with autonomic seizure findings

No./sex/age (years) antibody[a]; level	IHC[b]	Age at onset (years)	Epilepsy syndrome	Etiology	Personal history	Psychiatric features	Seizure types	Type of aura	AED response
1/M/31 NMDAR; 2	Positive	7	L TLE	MTLE/HS	Meningitis	Psychosis, depression	Focal, rarely SGS	Abdominal discomfort and pain	Poor
2/M/33 NMDAR; 3	Positive	20	L TLE	FEoUC	Difficult delivery	Postictal psychotic spells	Focal, SGS	Deja-vu feeling	Poor
3/M/39 NMDAR; 2	Negative	32	NL	FEoUC	Febrile seizures	Depression	Focal, SGS	Cephalic aura, nausea, palpitations	Good
4/M/57 NMDAR; 2	Positive	54	TLE	FEoUC	Benign prostatic hypertrophy, sensorial hearing loss	Obsessive–compulsive personality disorder	Focal, SGS	No aura	Poor
5/F/39 NMDAR; 2	Positive	8	NL	FEoUC	Hypothyroidism	Obsessive–compulsive disorder	Focal, SGS, SE	Peri-oral and lingual paresthesia	Poor
6/M/24 VGKC (80.50 pM)[c]	Positive	13	Bilateral TLE	MTLE/HS	Febrile seizures	Unremarkable	Focal, rarely SGS	Nausea, epigastric aura	Poor
7/M/26 VGKC (138.60 pM)[c]	Positive	8	Bilateral TLE	MTLE/HS	Head trauma, febrile seizures	Psychosis, suicidality	Focal, SGS	Nausea, palpitation, fear, fever	Good
8/F/57 VGKC (117.72 pM)[c]	Positive	12	R TLE	MTLE/HS	Unremarkable	Psychosis, suicidality, obsessive–compulsive personality disorder	Focal, rarely SGS, SE	Cardiac, abdominal tightness, anxiety	Poor
9/F/15 CASPR2; 2	Positive	7	NL	FEoUC	Hypothyroidism, obesity	Unremarkable	Focal, SGS	No aura	Poor
10/F/29 CASPR2; 2	Positive	16	L TLE	MTLE/HS	Migraine, febrile seizures	Obsessive–compulsive disorder	Focal	Nausea, epigastric aura, urinary urge	Poor
11/F/30 CASPR2; 3	Negative	10 months	Bilateral TLE	MTLE/HS	Birth trauma, Mental retardation	Unremarkable	Focal, SGS, SE	Water drinking, flushing, palpitation	Poor
12/M/35 CASPR2; 3	Positive	1	L TLE	MTLE/HS	Meningitis, febrile seizures	Depression	Focal, SGS	Epigastric aura, pilomotor aura, cold shivers	Poor
13/F/36 CASPR2; 3	Positive	20	NL	Cortical dysplasia	Unremarkable	Unremarkable	Focal	Fear, anxiety	Poor
14/F/37 GABA(A)R; 3	Positive	11	R TLE	MTLE/HS	Meningitis, febrile seizures	Depression, psychotic spells, postoperative hypersexuality	Focal, SGS, SE	Fear, pilomotor aura	Poor
15/F/26 GAD (2200 U/ml)[d]	Positive	10	TLE	Hypoxic birth injury	Migraine, difficult delivery, mental retardation	Unremarkable	Focal	Anxiety, deja-vu, jaime-vu	Poor
16/M/20 GAD (4100 U/ml)[d]	Negative	6	TLE	FeoUC	Type 1 diabetes, head trauma	Depression	Focal	Nausea, abdominal pain, flushing, deja-vu, change of sounds	Poor

Table 1 continued

No./sex/age (years) antibody[a]; level	IHC[b]	Age at onset (years)	Epilepsy syndrome	Etiology	Personal history	Psychiatric features	Seizure types	Type of aura	AED response
17/F/30 GLYR; 3	Positive	14	TLE	FeoUC	Head trauma, migraine	Depression	Focal, SGS, NCSE	Cephalic aura, nausea	Good

Patient 3, 7 and 17 were previously reported by Ekizoglu et al. [8]

AED antiepileptic drug, *CASPR2* contactin-associated protein-like 2, *F* female, *FEoUC* focal epilepsy of unknown cause, *GABA(A)R* gamma-aminobutyric acid type A receptor, *GAD* anti-glutamic acid decarboxylase, *GLYR* glycine receptor, *IHC* immunohistochemistry, *L* left, *M* male, *MTLE-HS* mesial temporal lobe epilepsy with hippocampal sclerosis, *NCSE* nonconvulsive status epilepticus, *NL* nonlocalized and lateralized, *NMDAR N*-methyl-D-aspartate receptor, *R* right, *TLE* temporal lobe epilepsy, *SE* status epilepticus, *SGS* secondarily generalized seizures, *VGKC* voltage-gated potassium channel

[a] Numbers indicate the antibody binding intensity scored visually on a range from 0 (negative) to 4 (very strong) in cell based assay (CBA)

[b] Hippocampal neuropil staining by immunohistochemistry

[c] Healthy control <50 pM, detections were performed by radioimmunoassays (RIA; RSR, Cardiff, UK)

[d] Healthy control <10 U/ml, detections were performed by radioimmunoassays (RIA; RSR, Cardiff, UK)

Discussion

Our current study revealed that 29.3 % of the chronic epilepsy patients with peri-ictal autonomic findings were positive for various NAAb. In our previous study performed with the same laboratory methodology, autonomic aura was detected in 53.8 % of the seropositive and 32.3 % of the seronegative patients [8]. Moreover, in a recent study, one (NMDAR antibody positive) out of seven autoimmune encephalitis patients was reported to have prominent dysautonomia [17]. These findings led us to design this new study with a larger number of patients with autonomic features. This current seropositivity result is higher than our other former study done with the same laboratory methodology, in which we found autoantibodies in one-sixth of the patients with focal epilepsy cohorts [8]. The most frequently found antibodies in the current study were against NMDAR and CASPR2 (29 %), followed by uncharacterized VGKC-complex antigens (18 %), GAD (12 %), GLYR and $GABA_AR$ (6 %). Remarkably, $GABA_AR$ antibody is reported for the first time in a chronic epilepsy patient with pilomotor seizures. Another novel finding of this study is the transient fever increase during seizures that are detected in association with VGKC-complex autoantibodies. Previous studies have reported the prevalence of NAAb in epilepsy cohorts ranging between 10 and 16 %; antibodies to VGKC-complex (including CASPR2 and LGI1), GLYR and NMDAR are the most frequently found autoantibodies in epilepsy patients [6–8].

Three patients with uncharacterized VGKC-complex antibodies (patient 6, 7 and 8) had significantly low antibody titers. Low VGKC-complex antibody levels are generally not believed to indicate a clinical significance and are considered to be merely a bystander indicator of presumable immune-mediated etiology. These patients were nevertheless considered here to be seropositive due to their serum IgGs' strong neuropil immunoreactivity (Fig. 1a, b), which implies that these patients might have coexisting and as yet uncharacterized neuronal surface antibodies. Even after excluding three patients with low titer VGKC-complex antibodies, our seropositivity prevalence is 24 % which is still higher than those of unselected epilepsy patient series and other previously reported epilepsy cohorts. Our cohort included patients with FEoUC, MTLE-HS and other structural causes of epilepsy and most of them had a poor response to AED. None of the seropositive patients showed acute or subacute onset of epilepsy or evidence of MRI abnormalities that are commonly observed in limbic encephalitis or any other antibody mediated neuroinflammatory disease. There was no association of seropositivity with respect to age, sex,

Table 2 Laboratory findings and management of seropositive patients

No.	MRI findings	PET findings	Ictal EEG findings	Autonomic findings during ictal EEG	AED at the sampling	Seizure frequency at the sampling	Treatment/prognosis
1	L HS	L T, Bi F L > R hypom	Invasive recording 4 sz from left T area	Tachycardia	TPM 100 mg	No sz	Engel 1 for 7 years after L temporal lobectomy
2	N	L T hypo	2 nonlocalised sz	Tachycardia	LEV 2000 mg, CBZ 800 mg	Deja-vu 1/day, SGS4/year	Rare focal sz (6/year) after LEV 3000 mg/day
3	R F NSSC	Not available	Not available	Not available	VPA 1000 mg	No sz	Sz free for 3 years
4	N	N	2 sz from R FT area, 2 nonlocalised sz	Postictal bradycardia, hypoventilation	LEV 2000 mg, ZNS 200 mg	Focal 1/month, SGS 2/year	Rare focal sz (4/year) under regular AED treatment
5	N	Not available	2 nonlocalised sz	Hypersalivation	OXC 1500 mg, TPM 200 mg	Focal 2/month	Non disabling sz (6/year) after VNS
6	Bilat HS	Bi T L > R hypom	20 focal sz, 4 sz from R FT area, others nonlocalised	Postictal documented transient unexplained fever	PB 100 mg, TPM 100 mg, LEV 2000 mg	Focal 4–5/month	Invasive EEG monitoring planned
7	Bilat HS	Bi T R > L hypom	Not available	Not available	LEV 3000	Focal 6/year	Rare focal sz under regular AED treatment
8	R HS	Bi T R > L hypom	5 sz from right FT area spread rapidly to left	Tachycardia, hypersalivation, postictal cough	LEV 1000 mg	No sz	Spontaneous remission, sz free for 4 years
9	N	R P hypom	7 nonlocalised sz	Postictal cough (ictal urination in history)	LEV 1000 mg, OXC 600 mg	Focal 6–10/month, SCG 2/month	Immunotherapy and VNS planned
10	L HS	Not available	3 sz from L FT	Nausea, retching, postictal cough, tachycardia	No AED	No sz	Engel 1 for 3 years after L amygdalohippocampectomy
11	Bilat HS, PO cortical atrophy	L T hypom	Not available	Not available	TPM 400 mg, LTG 500 mg, OXC 600 mg	Focal 2–3/month, SGS 4/year	Engel 4 for 9 years after L temporal lobectomy, immunotherapy planned
12	L HS	Bi T hypom	2 sz from L FT area, 1 nonlocalised sz	Pilomotor aura, tachycardia, genital automatism	CBZ 800 mg, LTG 400 mg	Focal 4–5/month	Engel 2 for 1 years after L temporal lobectomy
13	L T cortical dysplasia	Bi T hypom	2 nonlocalised sz	Tachycardia	LEV 3000 mg, LTG 200 mg, CBZ 1200 mg, PG 150 mg	Focal 4–10/month	Invasive EEG monitoring and immuntherapy planned
14	R HS	R T hypom	6 subclinic sz from R FT area	Not availabe	OXC 600 mg	No sz	Engel 1 for 8 years after right amygdalohippocampectomy
15	Posterior PV NSSC	R T hypom	2 nonlocalised sz	Tachycardia (spitting, urine and fecal incontinence in sz history)	LEV 3000 mg, CBZ 1000 mg, LTG 100 mg	Focal 4–5/month	Invasive EEG monitoring and immunotherapy planned

Table 2 continued

No.	MRI findings	PET findings	Ictal EEG findings	Autonomic findings during ictal EEG	AED at the sampling	Seizure frequency at the sampling	Treatment/prognosis
16	N	Not available	1 subclinic sz from left TO area	Not available	LTG 300 mg, VPA 1000 mg, LEV 1000 mg	Focal 15–20/month (in 1 day)	Stable
17	N	Not available	1 sz from right FT	Nausea	CBZ 800 mg	Focal 4/year	Sz free for 2 years

AED antiepileptic drug, *C* central, *CBZ* carbamazepine, *F* frontal, *FIRDA* frontal intermittent rhythmic delta activity, *HS* hippocampal sclerosis, *hypom*: hypometabolism, *IVMTP* intravenous methylprednisolone, *L* left, *LEV* levetiracetam, *LTG* lamotrigine, *MRI* magnetic resonance imaging, *N* normal, *NSSC* nonspecific subcortical signal change, *O* occipital, *OXC* oxcarbazapine, *P* parietal, *PB* phenobarbital, *PET* positron emission tomography, *PV* periventricular, *R* right, *SGS* secondarily generalized seizure, *sz* seizure, *T* temporal, *TIRDA* temporal intermittent rhythmic delta activity, *TPM* topiramate, *VPA* valproic acid, *VNS* vagal nerve stimulation, *ZNS* zonisamide

epilepsy duration and etiology, coexisting autoimmune disease and number of used AED or other managements. Thus, autonomic ictal findings may be listed as another possible new marker for screening NAAb.

In the group with FEoUC, most commonly detected antibody was NMDAR antibody whereas the frequency of antibodies directed to VGKC-complex (including CASPR2) was higher in MTLE-HS (17.6 %) group. To our knowledge, antibodies to $GABA_AR$ have been systematically screened for the first time in an epilepsy population. The overall prevalence of antibodies was higher in the group with FEoUC but not significantly different from symptomatic epilepsy group as opposed to Brenner et al. who found a significantly higher prevalence of positive antibody titers in patients with FEoUC, but this study also included patients with generalized epilepsy [6]. We identified GAD antibody in one patient with symptomatic epilepsy and another one with FEoUC. In the latter patient the presence of GAD antibody could be explained by the coexistence of type 1 DM. Both of these patients showed the electroclinical features of TLE.

Ictal piloerection is an infrequent autonomic semiology of focal seizures which have been mainly associated with an origin in the temporal lobe [25, 26]. There are individual reports on ictal piloerection which occurred multiple times per day as a clinical presentation of limbic encephalitis [4, 12, 13]. Ictal piloerection was reported as a semiological feature in the LGI1, Hu, Ma2, and VGKC-complex antibody seropositive limbic encephalitis patients, previously [4, 12, 13]. One of our patients was seropositive for CASPR2 antibody, another component of the VGKC-complex and the other one for $GABA_AR$ antibody, which has never been associated with pilomotor aura to our knowledge. Although two out of our three cases with pilomotor manifestations and TLE had NAAb, our sample size is too small to suggest a clear association with autoimmunity. Nevertheless, our findings prompt investigation of similar cases in clinical practice.

Three of our patients had peri-ictal fever which is a very rarely described seizure symptom. Reported patients with peri-ictal fever showed mostly bi-temporal EEG alterations as in our cases with bilateral MTLE-HS [27, 28]. Spread of interictal or ictal activity to thermoregulatory centers in hypothalamus and preoptic area may induce peri-ictal fever [28]. Intriguingly, patients who present with VGKC complex antibody positive limbic encephalitis frequently have unexplained febrile prodromes [29, 30]. The results of our study might suggest addition of "peri-ictal transient fever" to the list of possible markers of NAAb.

There is a recent suggestion that epileptic headache/pain should be added to "ictal autonomic manifestations" in forthcoming revisions of the ILAE classification [31]. In

Table 3 The comparison of seropositive and seronegative patients with peri-ictal autonomic symptoms

	Seropositive patients, $N = 17$ (%)	Seronegative patients, $N = 41$ (%)	p values
Sex (female/male)	9/8 (53/47)	28/13 (68/32)	ns
Age at serum sampling (years)	33.3 ± 10.6	34.6 ± 9.8	ns
Epilepsy duration (years)	19.1 ± 10.5	19.1 ± 9.2	ns
Poor AED response	14 (82)	38 (92)	ns
Febrile seizures	6 (35.2)	18 (44)	ns
Psychiatric disorders	11(64.7)	20 (48.7)	ns
Psychosis	5 (29.4)	2 (4.8)	0.01*
History of status epilepticus	5 (29.4)	2 (4.8)	0.01*
Family history of epilepsy	5 (29.4)	12 (29.2)	ns
Coexisting autoimmune disease	3 (17.6)	15 (36.5)	ns
Epilepsy etiology			
MTLE/HS	8 (47)	26 (63.4)	ns
Unknown	7 (41.1)	8 (19.5)	ns
Other symptomatic	2 (11.7)	7 (17)	ns
MRI findings			
Unilateral	6 (35.2)	26 (63.4)	ns
Bilateral	3 (17.6)	6 (14.6)	ns
Engel 1 outcome	3 (60)	13 (86.6)	ns
EEG findings			
Background slowing	3 (17.6)	7 (17)	ns
Bilateral epileptiform discharges	8 (53)	16 (43)	ns
Peri-ictal autonomic findings			
Tachycardia	7 (41.1)	20 (48.7)	ns
Brady-arrhythmia	1 (5.8)	0	ns
Epigastric aura	9 (52.9)	16 (39)	ns
Water drinking	1 (5.8)	8 (19.5)	ns
Cough	3 (17.6)	4 (9.7)	ns
Spitting	1 (5.8)	4 (9.7)	ns
Hypersalivation	2 (11.7)	7 (17)	ns
Piloerection	2 (11.7)	1 (2.4)	ns
Flushing	1 (5.8)	2 (4.8)	ns
Fever	2 (11.7)	1 (2.4)	ns
Genital automatism	1 (5.8)	3 (7.3)	ns
Urinary urge/urination	2 (11.7)	2 (4.8)	ns

AED antiepileptic drug, *MTLE-HS* mesial temporal lobe epilepsy with hippocampal sclerosis, *MRI* magnetic resonance imaging

* Fisher's exact test

our cohort two of our seronegative patients reported ictal and postictal headache whereas none of the seropositives displayed seizure-related headache.

Autonomic seizures mainly associate with an origin in the mesial temporal lobes and limbic system. As previously known, neuronal surface and GAD antibody associated encephalitis present mainly with temporal lobe epilepsy and MRI evidence of temporal lobe inflammation, which may suggest a reciprocal functional relationship between limbic circuits and autonomic responses [4, 5, 12, 13]. The exact underlying neuro-chemical correlates are not clear.

Psychotic disorders demonstrated significant associations with seropositivity as we also showed in our previous report [8]. Limbic encephalitis with NAAbs may associate with psychiatric features especially with psychosis [32]. Furthermore there are case reports of patients with a pure psychiatric phenotype who respond well to immunotherapies [33, 34]. Disruption of blood brain barrier (BBB) integrity in limbic or medial temporal regions due to seizures is hypothesized to cause access of pathogenic autoantibodies which exert functional effects on their target receptor that may lead to cognitive and behavioral changes

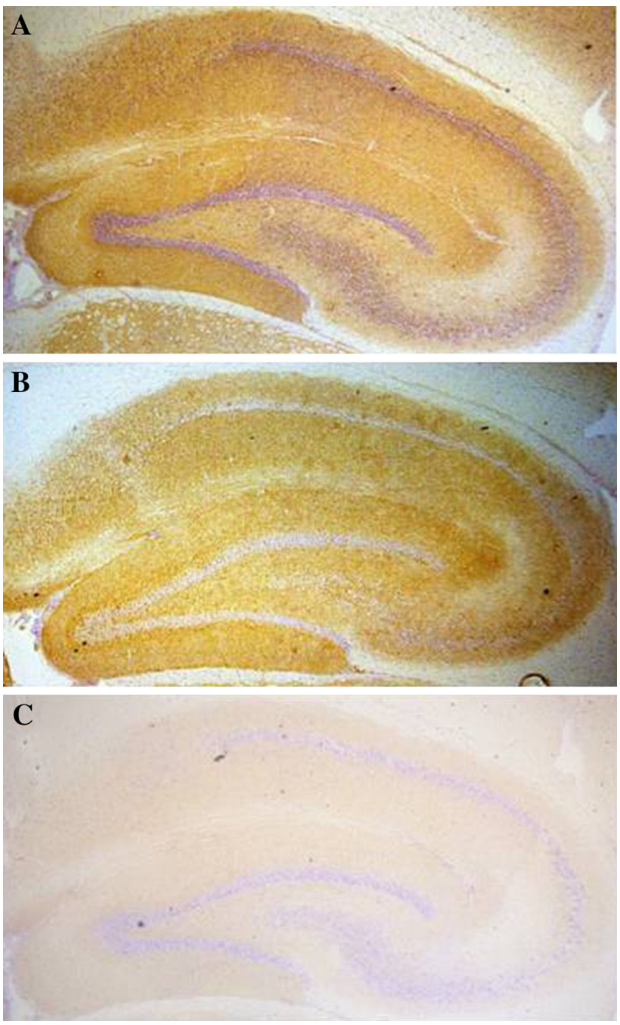

Fig. 1 Representative indirect immunohistochemistry results of seropositive (**a**, **b**) and seronegative (**c**) epilepsy patients. Serum IgGs of seropositive patients (patient 6 and 7) show strong reactivity with the hippocampal molecular layer, whereas no reactivity is observed with IgGs of the seronegative patient (original magnification ×40). Staining was performed with the avidin–biotin–peroxidase technique with hematoxylin counterstaining

of psychosis [35]. There are also reports demonstrating ongoing deep limbic/medial temporal epileptic activity correlating with psychosis [36, 37].

Although NMDAR antibody encephalitis is frequently reported in female patients with ovarian teratoma, four of our chronic epilepsy patients with NMDAR antibody were male, intriguingly [38]. Initial presentation of adult male patients with NMDAR antibody encephalitis is reported to be different from female patients, with more focal seizures at onset, development of behavioral and psychiatric features later during the course of disease and reduced association with tumors [10, 39]. The differences in hormonal influence could contribute to this unexplained difference in clinical pattern which needs further investigations [39].

In our series, EEG findings did not disclose any particular characteristics for seropositivity. Neither the presence nor localization of interictal epileptiform discharges and focal slow waves besides other periodic patterns such as PLEDs or FIRDA were significant predictors for seropositivity, as reported in our recent study [17]. Moreover, none of our patients with NMDAR seropositivity showed the reported extreme delta brush activity on the EEG [40]. Thus, EEG findings alone should not be considered as a marker of seropositivity.

Some previous reports showed that NAAb associated with encephalitis should be considered in the etiology of status epilepticus [11, 17, 41, 42]. Nearly one-third of the seropositive patients in our patient group had history of status epilepticus which is significantly more prevalent than seronegative patients, supplying further evidence for this particular association needing attention in daily practice.

In the last follow up, nearly half of the seropositive patients were seizure-free and three had good functional status after changes in AED treatments. Therefore, although some of the seropositive patients may be refractory to AED treatment, this association with NAAb seems compatible with good functioning in daily life in 65 % of the patients with chronic epilepsy. Two seropositive AED-resistant patients who had GAD and CASPR2 antibodies showed no benefit from corticosteroids. Malter et al. observed poor responsiveness of seizures to immunotherapies in a group of patients with GAD-TLE which suggested that these antibodies are related with a T-cell mediated immunopathology rather than humoral immune response [43, 44]. A clear response to immunotherapy would help to solve the question whether these antibodies present as an immunological epiphenomenon [43].

It is highly likely that the presence of NAAb in symptomatic etiologies like tumors or focal cortical dysplasia may occur as an epiphenomenon which is secondary to structural changes or seizure related excitotoxicity. However, there might be still a subgroup of epileptic patients who indeed have acute and active inflammation in the brain needing further scientific attention. The detection of NAAb is not enough to uncover the full picture and should be supported by other tools like advanced neuro-imaging.

Our study showed no association with mean epilepsy duration and the presence of various NAAb which corroborates our previous results [8]. On the contrary, mean epilepsy duration was found shorter in a group of patients with GAD antibody positive cryptogenic focal epilepsy compared to patients who were seronegative [45]. By contrast, in a previous study the presence of NAAb was found to be equally common in newly diagnosed and established epilepsies [6]. Therefore, it seems unlikely that the presence of these antibodies is solely an

epiphenomenon of long standing chronic epilepsy [6, 8]. Interestingly only a single NAAb was detected in an individual patient, in our study. Many different NAAb would be expected if antibody occurrence was a bystander effect due to neuronal damage and concomitant BBB damage. Likewise, in autoimmune encephalitis patients with NAAb we usually detect a single antibody with a specific mechanism of action. Thus, absence of multiple antibodies in the same patient may further suggest that chronic epilepsy may occur as a result of specific anti-neuronal immunity in this selected group.

The main strengths of our study is the first time systematic screening of nine NAAb, in a well-characterized epilepsy population with peri-ictal autonomic findings and detailed evaluation of clinical, neuroradiologic and EEG findings. Some associations like peri-ictal fever associated with VGKC antibodies and pilomotor seizures with $GABA_AR$ antibodies were described for the first time in our study. Main limitations are its retrospective design and lack of video-EEG recordings in a minority of patients with rare seizures. Our cohort could be criticized as being moderate-sized and heterogeneous which are unavoidable in this rare entity with autonomic semiology. We selected majority of the patients among chronic epilepsy patients; hence this may have biased us towards more treatment resistant epilepsies increasing the likelihood of seropositivity. Additional supportive features like cerebrospinal fluid data and response to immunotherapy are needed to demonstrate the possible relation of autoimmune etiology and epilepsy. Moreover, there are no long-term follow-up of the patients who received immunotherapy, which we plan to study prospectively.

In conclusion; we detected a high prevalence of NAAb positivity in patients with chronic epilepsy with autonomic semiology. Antibodies against VGKC-complex and NMDAR were the leading ones. Presence of peri-ictal fever and pilomotor aura in patients with epilepsy may prompt investigation for autoimmunity. Presence of status epilepticus and psychotic attacks in patients' history are strongly related with seropositivity. It remains still unclear whether antibodies are primarily pathogenic or occur as a secondary response to neuronal damage related to seizures. Further studies are needed for the interpretation of the benefit from the immunotherapy in chronic epilepsy patients who have NAAb.

Acknowledgments Our study was supported by the Turkish Scientific and Technical Research Council with a number of 214S170 and Istanbul University Research Fund with a number BAP-39616.

Compliance with ethical standards

Conflicts of interest None of the authors has any conflict of interest to disclose.

Ethical standards The study was approved by the ethics committee.

References

1. Shorvon S, Frederick A, Renzo G (2011) The causes of epilepsy: common and uncommon causes in adults and children. Cambridge University Press, Cambridge
2. McKnight K, Jiang Y, Hart Y, Cavey A, Wroe S, Blank M et al (2005) Serum antibodies in epilepsy and seizure-associated disorders. Neurology 65:1730–1736
3. Majoie HJ, de Baets M, Renier W, Lang B, Vincent A (2006) Antibodies to voltage-gated potassium and calcium channels in epilepsy. Epilepsy Res 71:135–141
4. Quek AM, Britton JW, McKeon A, So E, Lennon VA, Shin C et al (2012) Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 69:582–593
5. Liimatainen S, Peltola M, Sabater L, Fallah M, Kharazmi E, Haapala AM et al (2010) Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. Epilepsia 51:760–767
6. Brenner T, Sills GJ, Hart Y, Howell S, Waters P, Brodie MJ et al (2013) Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia 54:1028–1035
7. Suleiman J, Wright S, Gill D, Brilot F, Waters P, Peacock K et al (2013) Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies. Epilepsia 54:2091–2100
8. Ekizoglu E, Tuzun E, Woodhall M, Lang B, Jacobson L, Icoz S et al (2014) Investigation of neuronal autoantibodies in two different focal epilepsy syndromes. Epilepsia 55:414–422
9. Irani SR, Buckley C, Vincent A, Cockerell OC, Rudge P, Johnson MR et al (2008) Immunotherapy-responsive seizure-like episodes with potassium channel antibodies. Neurology 71:1647–1648
10. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS et al (2010) *N*-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly nonparaneoplastic disorder of both sexes. Brain 133:1655–1667
11. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M et al (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7:1091–1098
12. Wieser S, Kelemen A, Barsi P, Vincent A, Borbely C, Rasonyi G et al (2005) Pilomotor seizures and status in non-paraneoplastic limbic encephalitis. Epileptic Disord 7:205–211
13. Rocamora R, Becerra JL, Fossas P, Gomez M, Vivanco-Hidalgo RM, Mauri JA et al (2014) Pilomotor seizures: an autonomic semiology of limbic encephalitis? Seizure 3:670–673
14. Barber PA, Anderson NE, Vincent A (2000) Morvan's syndrome associated with voltage-gated K^+ channel antibodies. Neurology 54:771–772
15. Liguori R, Vincent A, Clover L, Avoni P, Plazzi G, Cortelli P et al (2001) Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. Brain 124:2417–2426
16. Zuliani L, Graus F, Giometto B, Bien C, Vincent A (2012) Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry 83:638–645
17. Baysal-Kirac L, Tuzun E, Altindag E, Ekizoglu E, Kinay D, Bilgic B et al (2015) Are there any specific EEG findings in autoimmune epilepsies? Clin EEG Neurosci. doi:10.1177/1550059415595907 **(in press)**

18. Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr (2001) Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia 42:1212–1218
19. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W et al (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 51:676–685
20. Kwan P, Arzimanoglu A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G et al (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE commission on therapeutic strategies. Epilepsia 51:1069–1077
21. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L et al (2010) Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain 133:2734–2748
22. Pettingill P, Kramer HB, Coebergh JA, Pettingill R, Maxwell S, Nibber A et al (2015) Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. Neurology 84:1233–1241
23. Waters P, Woodhall M, O'Connor KC, Reindl M, Lang B, Sato DK et al (2015) MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm 2:e89
24. Zandi MS, Paterson RW, Ellul MA, Jacobson L, Al-Diwani A, Jones JL et al (2015) Clinical relevance of serum antibodies to extracellular *N*-methyl-D-aspartate receptor epitopes. J Neurol Neurosurg Psychiatry 86:708–713
25. Stefan H, Pauli E, Kerling F, Schwarz A, Koebnick C (2002) Autonomic auras: left hemispheric predominance of epileptic generators of cold shivers and goose bumps? Epilepsia 43:41–45
26. Dove GH, Buchhalter JR, Cascino GD (2004) Acute repetitive pilomotor seizures (goose bumps) in a patient with right mesial temporal sclerosis. Clin Neurophysiol 115:2511–2513
27. Meo R, Bilo L, Striano S, Ruosi P, Estraneo A, Nocerino C (1995) Transient global amnesia of epileptic origin accompanied by fever. Seizure 4:311–317
28. Rossetti AO, Tosi C, Despland PA, Staedler C (2007) Post-ictal fever: a rare symptom of partial seizures. Eur J Neurol 14:586–590
29. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N et al (2004) Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 127:701–712
30. Thieben M, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S (2004) Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. Neurology 62:1177–1182
31. Parisi P, Striano P, Villa MP, Belcastro V (2013) Ictal epileptic headache: terms do matter in clinical practice! Reply to Cianchetti et al. Cephalalgia 33:426
32. Titulaer MJ, McCracken L, Gabilondo L, Armangué T, Glaser C, Iizuka T et al (2013) Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12:157–165
33. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J (2013) Frequency and characteristics of isolated psychiatric episodes in anti-*n*-methyl-D-aspartate receptor encephalitis. JAMA Neurol 70:1133–1139
34. Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P et al (2011) Disease-relevant autoantibodies in first episode schizophrenia. J Neurol 258:686–688
35. Pollak TA, Nicholson TR, Mellers JD, Vincent A, David AS (2014) Epilepsy-related psychosis: a role for autoimmunity? Epilepsy Behav 36:33–38
36. Kuba R, Brazdil M, Rektor I (2012) Postictal psychosis and its electrophysiological correlates in invasive EEG: a case report study and literature review. Epilepsy Behav 23:426–430
37. Takeda Y, Inoue Y, Tottori T, Mihara T (2001) Acute psychosis during intracranial EEGmonitoring: close relationship between psychotic symptoms and discharges in amygdala. Epilepsia 42:719–724
38. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A et al (2007) Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61:25–36
39. Viaccoz Desestret V, Ducray F, Picard G, Cavillon G, Rogemond V et al (2014) Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. Neurology 82:556–563
40. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D (2012) Extreme delta brush a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 79:1094–1100
41. Johnson N, Henry C, Fessler AJ, Dalmau J (2010) Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. Neurology 75:1480–1482
42. Kirkpatrick MP, Clarke CD, Sonmezturk HH, Abou-Khalil B (2011) Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis. Epilepsy Behav 20:392–394
43. Malter MP, Frisch C, Zeitler H, Surges R, Urbach H, Helmstaedter C et al (2015) Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies. Seizure 30:57–63
44. Bien CG, Vincent A, Barnett MH, Becker AJ, Blümcke I, Graus F et al (2012) Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain 135:1622–1638
45. Errichiello L, Perruolo G, Pascarella A, Formisano P, Minetti C, Striano S et al (2009) Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: a study on 233 patients. J Neuroimmunol 211:120–123