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Are There Any Specific EEG Findings in Autoimmune Epilepsies?

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Abstract

This study evaluated the EEG findings of patients whose seizures were associated with a possible autoimmune etiology. Our aim was to find clues to distinguish patients with antineuronal antibodies (Ab) through EEG studies. We reviewed our database and identified antineuronal Ab positive epilepsy patients with or without autoimmune encephalitis. These patients had Abs to *N*-methyl-D-aspartate receptor (NMDAR) (n = 5), glycine receptor (GLY-R) (n = 5), contactin-associated protein-like 2 (CASPR-2) (n = 4), uncharacterized voltage-gated potassium channel complex (VGKC) antigens (n = 2), glutamic acid decarboxylase (GAD) (n = 2), Hu (n = 1), and amphiphysin (n = 1). The control group consisted of 21 seronegative epilepsy or encephalopathy patients with similar clinical features. EEG findings were compared between the groups in a blindfolded design. We did not find any significant difference in EEG findings between antineuronal Ab positive epilepsy patients and seronegative control group. It was remarkable that four seropositive but none of the seronegative patients presented with nonconvulsive status epilepticus (NCSE) or focal motor status epilepticus. Continuous theta and delta rhythms were observed in 5 (71%) seropositive patients with autoimmune encephalitis and 2 (25%) seronegative patients. Eight (40 %) seropositive patients showed a frontal intermittent rhythmic delta activity (FIRDA) pattern as opposed to 5 (24%) seronegative patients. Two patients with NMDAR Ab positivity showed rhythmic delta waves superimposed with beta frequency activity resembling "delta brush" pattern. EEG seems as a limited diagnostic tool in differentiating epilepsy and/or encephalopathy patients with a possible autoimmune etiology from those without. However, antineuronal Abs associated with encephalitis should be considered in the etiology of status epilepticus forms. A possible autoimmune etiology for seizures may be considered in the presence of continuous slow waves, FIRDA, and delta brush pattern in the EEG.

Keywords

autoimmune epilepsy, limbic encephalitis, nonconvulsive status epilepticus, EEG

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Introduction

The autoimmune encephalitis is a group of syndromes with subacute onset of amnesia, confusion and prominent seizures which may have paraneoplastic or immune-mediated etiology.[1] Nearly half of the patients diagnosed with limbic encephalitis have experienced seizures. Epileptic seizures and faciobrachial dystonia can precede the appearance of cognitive problems by several months.[2,3] Additionally, some specific antineuronal antibodies (Abs) with pathogenic potential may be present in a subset of patients with drug-resistant or even drug-responsive forms of focal epilepsy, including those lacking a typical "limbic encephalitis" phenotype.[1,4-7] These recent findings underpinned the new term "epilepsy with a possible autoimmune etiology." In these subjects epilepsy may be a direct result of the primary disease pathology or could be secondary to the pro-inflammatory process that is involved.[8]

EEG investigations besides magnetic resonance imaging (MRI) are widely used in the evaluation of autoimmune encephalitis and epilepsy. EEG changes are useful to evaluate the severity and localization of encephalopathy, to look for interictal epileptiform or seizure activity and to monitor patients with prolonged encephalopathy for a potential contribution of nonconvulsive status epilepticus (NCSE).[9] However, profound details on EEG are lacking in most of the studies related with encephalitis and

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epilepsy with a possible autoimmune origin. We, therefore, performed a retrospective study to analyze the EEG findings of patients whose seizures are associated with a possible autoimmune etiology. Additionally we aimed to find clues to distinguish patients with antineuronal Ab positivity through EEG studies.

Methods

Our database included 20 consecutive antineuronal Ab positive patients with EEG investigations (11 women, 9 men, mean age ± standard deviation 40.1 ± 14.3 years; range 19-76 years) who had been followed up or consulted with the Istanbul University Epilepsy Center over 5 years (2007-2012). The study was approved by the local ethics committee.

Selection Criteria

Inclusion criteria for this retrospective study were the following: (1) detection of an antineuronal Ab, (2) having at least 1 EEG and MRI performed during their evaluation, and (3) a clinical presentation consistent with seizures and/or neuropsychiatric manifestations associated with EEG abnormalities as the main reason for admission. The patients with obvious provoking factors or an apparent remote origin, such as a brain malformation or tumor, trauma, central nervous system (CNS) infection with MRI evidence, or all forms of genetic epilepsy syndromes were excluded. We reviewed the medical records of all patients included in the study. Information regarding demographic data, clinical presentation, neurological symptoms, laboratory data, including cerebrospinal fluid (CSF), whenever indicated for clinical purposes and neuroimaging findings, presence or absence of a tumor, response to treatment and detailed EEG data were collected for all subjects, retrospectively. All MRI studies were performed with 1.5-T scanners with thin coronal, sagittal and axial planes, including T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images and evaluated by an experienced neuroradiology team.

Patient and Control Groups

(a) Thirteen of the patients had only established chronic epilepsy associated with antineuronal Ab, and have been reported previously.[7] In this former study, all consecutive adult patients diagnosed with focal epilepsy of unknown cause or mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) followed by our epilepsy center for more than one year were screened for accompanying neuronal Ab to establish the prevalence of these antibodies in a cohort of 81 patients.[7] Among them, 7 patients who had been diagnosed with focal epilepsy of unknown cause and 6 with MTLE-HS have presented neuronal Ab and were included in the current EEG analysis.

(b) The other 7 included patients were diagnosed with acute/subacute onset of "possible autoimmune encephalitis." In our center's routine diagnostic protocol, we screened neuronal Abs, for clinical indications of unexplained acute/subacute onset of seizures or other encephalopathic symptoms and evidence for CNS inflammation either in the CSF (done in every unexplained case with this clinical picture if not rejected by the patients) or on MRI when other causes are excluded, according to the suggested criteria by Zuliani et al.[10] Tumor investigation, including thoracoabdominal computed tomography (CT) and/or whole body positron emission tomography (PET), was performed for all patients with autoimmune encephalitis.

(c) The control group for EEG analysis was selected as a total of 21 seronegative patients (13 women, 8 men, mean age ± standard deviation 40.5 ± 17.1 years; range 19-83 years) matched for age, gender, clinical presentation, and epilepsy syndrome. Thus, the control group consisted of 13 patients with chronic epilepsy only (5 patients with focal epilepsy of unknown cause, 6 patients with MTLE-HS, and 2 patients with viral limbic encephalitis) and 8 patients who presented with altered mental status/delirium and diagnosed with moderate to severe encephalopathy associated with metabolic dysfunction due to hepatic encephalopathy, uremia, or marked electrolyte imbalance.

EEG Analysis

Digital EEG recordings and EEG reports of all patients were reviewed and the findings were compared between seropositive and seronegative groups. All routine EEGs were 21-channel recordings acquired using 10-20 system for electrode placement. EEGs evaluated systematically for diffuse slowing, focal slowing, paroxysmal activities, and frontal intermittent rhythmic delta activity (FIRDA), epileptiform discharges, periodic EEG patterns, electrographic seizure activity and other findings, including "delta brush" pattern as reported by Schmitt et al[11] and fast activities. FIRDA was defined as predominantly frontal delta activity (1-4 Hz) lasting at least 2 seconds.[12] EEG findings were interpreted by two epileptologists independently. One of the reviewers was blindfolded to the diagnosis of the patients. The EEGs of the patients were included for further analysis by another senior epileptologist and any disagreements were resolved by consensus meeting after reviews.

In seropositive patients with possible autoimmune encephalitis and control group of patients with encephalopathy associated with metabolic conditions, 83% of all EEGs were performed in the acute/subacute stage (all had at least 1 EEG in this stage) and 17% were performed in chronic stage as control investigations of the disease course. Six out of 7 patients with autoimmune encephalitis were treated with antiepileptic drugs and 5 out of 7 were treated with immunosuppressive treatment as seen in Table 1. In patients with only established epilepsy, the EEGs were performed in chronic stage of the disease. All the patients

Table 1. Clinical and Laboratory Characteristics of the Patients With Autoimmune Encephalitis Associated With Various Autoantibodies.

Patient No./ Sex/Age (Years)	Antibody[a]	Presentation and Main Symptoms	History of Autoimmunity or Cancer	Seizure Types	CSF	MRI Findings	EEG Findings	Treatment	Prognosis
1/F/36	Anti-Hu, 3	Sensorial ataxia, seizures with experiential aura	In situ ductal breast tm	Focal and SGC	Normal WBC and protein concentration	Right fronto-orbital and insular cortex high T2 and FLAIR signal	Right FT theta waves and spikes, right FT subclinical seizures,[b] right PLED	AE: LEV, VPA, ZNS IS: IVIG, IVMTP, cyclophosphamide, AZO, PEX, mycophenolate	Uncontrolled seizures
2/M/58	Anti-amphiphysin, 2	Seizures, axonal type PNP	Bladder tm	SGC	Normal WBC and protein concentration	Bilateral frontal gliotic nonspecific lesions	Continuous theta/delta slow waves, right FT theta and sharp waves, delta paroxysms, fast activity	AE: PHT, LEV, OXC, PHB	Seizure responded to AE
3/F/22	Anti-NMDAR, 3	Right focal motor status, dysautonomia, facial dyskinesia, somnolence	Ovarian teratoma	Focal motor status, SGC	18 WBC/μL Increased protein	Normal	Continuous theta/delta slow waves, FIRDA, delta paroxsyms, delta brush	AE: PHT, CBZ, LEV, VPA	No response, exitus
4/M/58	Anti-NMDAR, 3	Psychosis, confusion, bradykinesia	None	Non-convulsive seizures	Normal WBC and protein concentration	Normal	Intermittent theta/delta slowing, FIRDA, Left T isolated spikes and theta slow waves, delta paroxysms, delta brush, fast activity	IS: IVIG, IVMTP	Substantial improvement
5/M/76	Anti-NMDAR, 2	Altered mental status, comatose state after seizures	Hashimoto thyroiditis, ankylosing spondylitis	NCSE	Increased protein	Bilateral subdural hematoma, hydrocephalus	Continuous theta/delta slow waves with superimposed 1.5-2 Hz rhythmical spike and wave activity, FIRDA, bilateral FT sharp waves and spikes, triphasic waves, bi-PLED	AE: DZ, PHT, LEV IS: IVMTP, PEX	Exitus
6/F/63	Anti-GAD (2127 U/mL)[c]	Psychosis, somnolence	None	NCSE	Normal WBC and protein concentration type 3 OCB	Normal	Continuous theta slow waves, nearly continuous 1.5-2 Hz rhythmical spike and wave activity	AE: VPA, PHT IS: IVIG, IVMTP	Substantial improvement
7/F/26	Anti-GAD (5000U/ml)[c] Anti-recoverin, 2	Somnolence, confusion	None	NCSE	Normal WBC and protein concentration	Bilateral temporal cortical high T2 and FLAIR signal	Continuous theta/delta slow waves, FIRDA, bilateral FT independent subclinical seizures	AE: VPA, LEV IS: IVMTP, IVIG	Substantial improvement

Abbreviations: AE, antiepileptic; M, male; F, female; CSF, cerebrospinal fluid; FIRDA, frontal intermittent rhythmic delta activity; FT, frontotemporal; T, temporal; PLED, periodic lateralized epileptiform discharges, bi-PLED, bilateral, independent, periodic, lateralized epileptiform discharge; SGC, secondarily generalized convulsions; IS, immunosupressive; CBZ, carbamazepine; LEV, levetiracetam; VPA, valproic acid; ZNS, zonisamide; PHT, phenytoin; DZ, diazepam; OXC, oxycarbazapine; IVIG, intravenous immunoglobulin; IVMTP, intravenous methylprednisolone; PEX, plasmapheresis; AZO, azathioprine; NMDAR, *N*-methyl-D-aspartate receptor; anti-GAD, anti–glutamic acid decarboxylase; MRI, magnetic resonance imaging; PET, positron emission tomography; tm, tumor; WBC, white blood cells; OCB, oligoclonal bands; PNP, polyneuropathy; NCSE, nonconvulsive status epilepticus.

[a]Numbers indicate the antibody binding intensity scored visually on a range from 0 (negative) to 4 (very strong).

[b]Figure 5.

[c]Healthy control <10 U/mL.

with epilepsy were taking antiepileptic drugs during EEGs. Immunotherapy was used with success for 3 out of 7 patients who had poor response to antiepileptic drug treatment.[7]

Autoantibody Testing

All patients and controls were tested for serum antibodies to voltage-gated potassium channel (VGKC)-complex antigens, glutamic acid decarboxylase (GAD), *N*-methyl-D-aspartate receptor (NMDAR), glycine receptor (GLY-R), contactin-associated protein-like 2 (CASPR-2), leucine-rich glioma inactivated 1 (LGI1), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor (AMPAR), Hu, Yo, Ma2, CV2, Ri, and amphiphysin. Sera from all patients were kept at 80°C until assayed. Ion channel antibodies were detected by binding to HEK293 cells transfected with plasmids containing the NR1/NR2 subunits of the NMDAR, GluR1/GluR2 subunits of the AMPAR, LGI1, CASPR-2, or GLY-R α1 subunit. Transfected cells were incubated with patients' sera (1:20) and the appropriate Alexa Fluor secondary Ab, as described earlier.[6,13,14] The binding was scored visually on a range from 0 (negative) to 4 (very strong) as in previous studies.[13] Only scores greater than 1 were accepted as positive to avoid nonspecific low positivity. For VGKC-complex antibodies, radioimmunoassay (RIA) using brain extracts labeled with ^{125}I-dendrotoxin (normal value <100 pM) were used.[13,15] GAD antibodies were measured by immunoprecipitation of ^{125}I-recombinant GAD (normal value <10 U/mL).[16] Commercially available immunoblots were used to test for paraneoplastic antibodies directed against Hu, Yo, Ri, amphiphysin, CV2, and Ma2 according to the manufacturer's instructions (Euroimmun, Lübeck, Germany). Blot strips were digitalized using a flatbed scanner and band intensities were evaluated by a software (EUROLineScan, Euroimmun). Ab binding was scored on a range from 0 (negative) to 4 (very strong), as recommended by the manufacturer.

Positive Ab results included NMDAR (n = 5), GLY-R (n = 5), CASPR-2 (n = 4), uncharacterized VGKC-complex antigens (n = 2), GAD (n = 2), Hu (n = 1), and amphiphysin (n = 1) antibodies. One of the GAD Ab positive patients also had recoverin Ab. Autoimmune encephalitis patients (n = 7) displayed NMDAR (n = 3) (with Ab binding scores ranging from 2 to 3), GAD (n = 2) with a titer of 2127 and 5000 U/mL, Hu (n = 1) (with Ab binding score of 3) and amphiphysin (n = 1) (with Ab binding score 2) Abs, whereas chronic epilepsy patients (n = 13) displayed Abs to GLY-R (n = 5) (with Ab binding scores ranging from 2 to 4), CASPR-2 (n = 4) (with Ab binding scores ranging from 2 to 3), NMDAR (n = 2) (with Ab binding scores of 2) and uncharacterized VGKC-complex antigens (n = 2) with titers of 201.4 and 138.6 pM.

Statistical Analysis

Fisher's exact test allowed comparisons of categorical variables in EEG parameters between patients with and without serum auto-Abs. Results were considered statistically significant when $P < 0.05$. Interrater reliability was computed using kappa (κ) statistics.

Results

Clinical Characteristics

Table 1 summarizes the clinical and laboratory findings of 7 patients with autoimmune encephalitis. Two patients presented with focal and secondary generalized seizures (SGS). Remaining 5 patients presented with altered mental status, mood, and behavioral changes. Three of them were diagnosed with NCSE after EEG examinations; in another one of them nonconvulsive seizures were suspected but could not be confirmed. The last patient developed right focal motor status epilepticus and then progressed into coma. Other associated neurological manifestations were sensorial ataxia (1), polyneuropathy (2), dysautonomia (1), and movement disorders (2). Three patients had histologically confirmed cancer diagnosis, as seen in Table 1. Patient 6 with NCSE was previously reported by Cikrikcili et al.[17]

Full details of the remaining 13 seropositive patients who were diagnosed with chronic epilepsy associated with neuronal Ab were given in a previous report.[7]

Psychiatric disorders depression and psychotic spells were associated with 11 (52%) of the seropositive group. MRI hyperintensities involving neocortex (frontal and temporal), subcortical white matter or mesial temporal lobes were identified in 13 patients. Eight patients (38%) had normal MRI. CSF analysis was performed in all of 7 patients with autoimmune encephalitis and was abnormal in 3 (43%) of them.

EEG Findings

Sixty-eight EEG investigations for seropositive patient group and 58 EEG investigations for seronegative control group were available for review. The mean number of EEGs per subject was 3 (range 1-6). All subjects had at least one abnormal EEG. All patients had at least one follow up EEG recorded between 2 days and 3 years after the initial presentation of clinical symptoms. Prolonged EEG monitoring was available in 7 out of 20 seropositive patients. The interrater variability in the assessment of EEGs was strong ($\kappa = 0.7$) between the blind and primary reviewers.

EEG findings of the study groups are summarized in Table 2 for both epilepsy and encephalitis subgroups separately. Epileptiform activity defined as either sharp waves or spikes was seen in 18 patients (90%) in the seropositive group. Eight patients (40%) showed FIRDA pattern (Figure 1). Periodic discharges including periodic lateralized epileptiform discharges (PLEDs), periodic epileptiform discharges (PEDs), and triphasic waves were seen in 3 patients (15%). We did not find any significant difference in EEG findings between seropositive patient and seronegative control group. Nevertheless, when compared with the seronegative group, seropositive patients were more inclined to display continuous slow waves, FIRDA, and epileptiform discharges and were less likely to exhibit intermittent slow waves (Table 2).

EEGs of 3 patients with autoimmune encephalitis were recorded during NCSE (Figures 2 and 3). EEGs showed

Table 2. Comparison of EEG Findings of Patients With and Without Antineuronal Antibodies.

	Seropositive Patients (n = 20)		Seronegative Patients (n = 21)		*P* Value for Seropositive vs Seronegative
	Epilepsy n = 13 (%)	Encephalitis n = 7 (%)	Epilepsy n =13 (%)	Encephalopathy n = 8 (%)	
No. of EEGs	41	27	45	13	
No. of abnormal EEGs	38	27	42	13	
Intermittent theta/delta slowing	5 (38)	2 (29)	8 (61)	6 (75)	0.06
Continuous theta/delta slowing	—	5 (71)	—	2 (25)	0.24
Focal slowing	6 (46)	5 (71)	8 (61)	2 (25)	0.76
FIRDA	4 (31)	4 (57)	3 (23)	2 (25)	0.33
Periodic discharges	1 (8)	2 (29)	—	1 (12)	0.34
Epileptiform discharges	12 (92)	6 (86)	9 (69)	4 (50)	0.06
Delta brush	—	2 (29)	—	—	ND
Fast activity	4 (31)	2 (29)	4 (31)	2 (25)	1.0
Focal seizures	6 (46)	1+focal status	6 (46)	—	1.0
NCSE	—	3 (43)	—	—	ND

Abbreviations: NCSE, nonconvulsive status epilepticus; FIRDA, frontal intermittent rhythmic delta activity; ND, not determined.

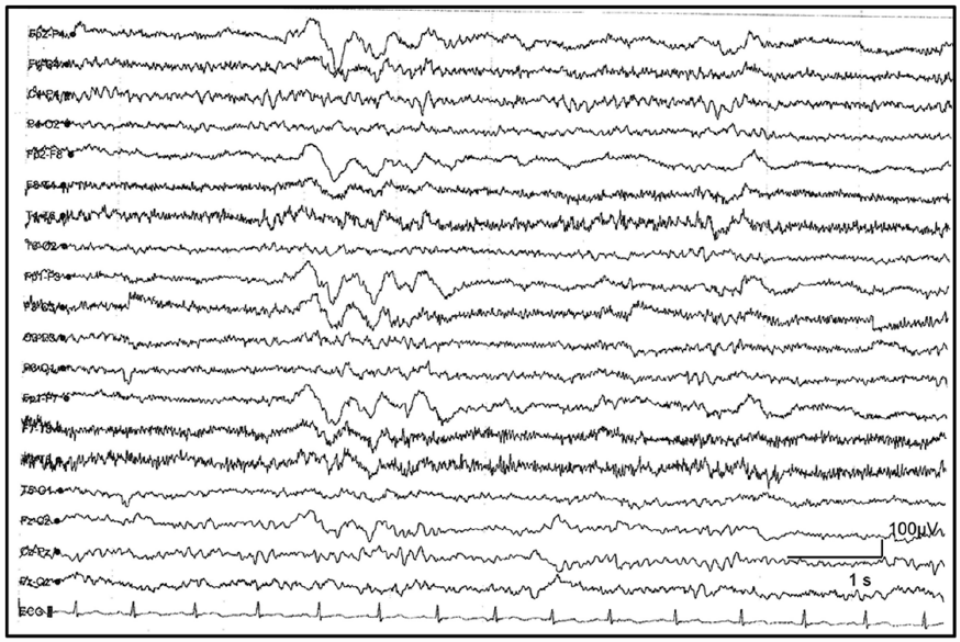

Figure 1. EEG example of an epilepsy patient with GLYR antibody. Frontal predominant 2- to 2.5-Hz delta activity, which lasts about 2 seconds (frontal intermittent rhythmic delta activity [FIRDA]).

continuous delta wave slowing with 1.5- to 2-Hz rhythmic spike-wave activity predominating over the anterior or posterior regions of 2 hemispheres. In some of the recordings of 2 patients with NMDAR Ab positivity, we observed rhythmic delta waves superimposed with beta frequency activity resembling delta brush pattern (Figure 4). NCSE and delta brush-like pattern in EEG were detected only in autoimmune encephalitis group.

Three patients with autoimmune encephalitis demonstrated gradual EEG improvement after immunotherapy, which was associated with clinical improvement (Table 1).

Discussion

We described the EEG features of consecutive patients who presented with seizures or encephalopathy related to a possible autoimmune etiology with different neuronal Ab. Three patients with autoimmune encephalitis presented with NCSE, and one further patient with focal motor status epilepticus which may illustrate the need to consider neuronal Ab–associated encephalitis as a cause of status epilepticus forms. We showed that EEG is a limited diagnostic tool in differentiating subjects whose seizures associated with a possible autoimmune etiology. However

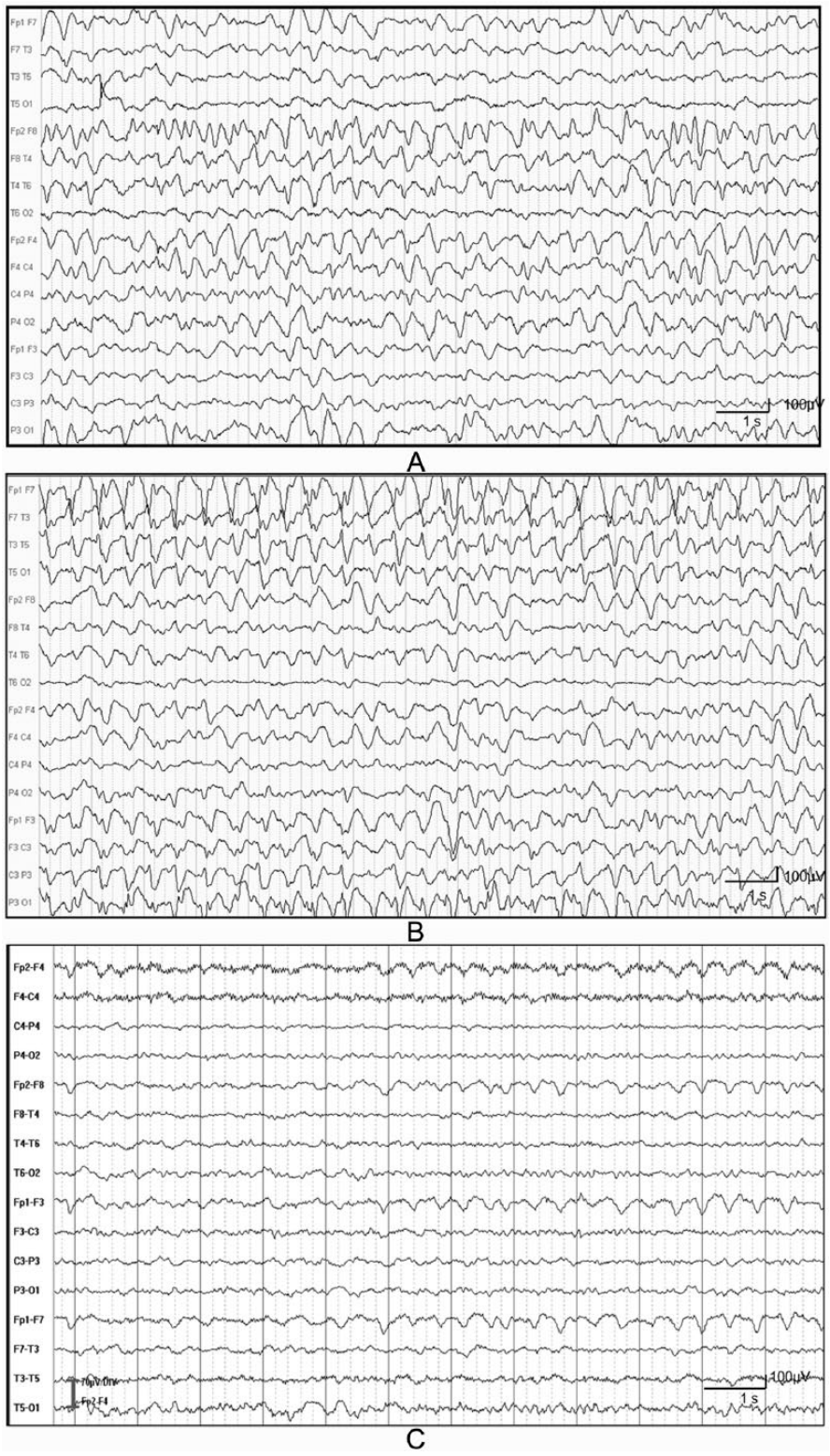

Figure 2. Nonconvulsive status epilepticus associated with anti–glutamic acid decarboxylase (anti-GAD) and anti-recoverin antibodies in patient 7. (A, B) EEG examples demonstrate continuous rhythmic 2-2.5 Hz bilateral independent frontotemporal seizure activities. (C) EEG and clinical findings improve markedly after IVIg (intravenous immunoglobulin) treatment, even though there were no response to previous antiepileptic drugs and IV pulse treatment.

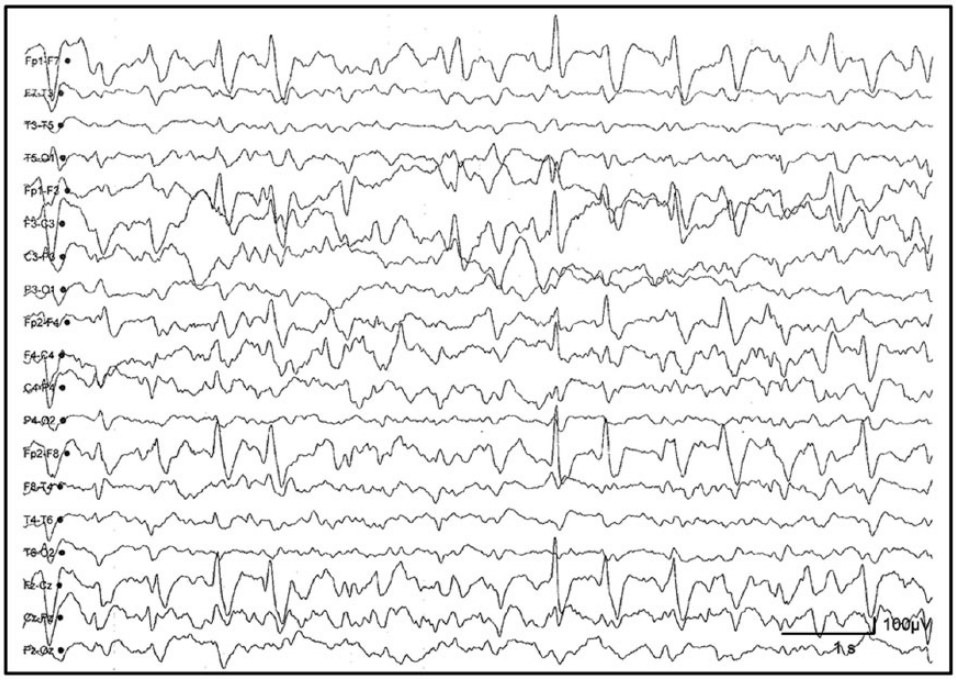

Figure 3. Nonconvulsive status epilepticus associated with *N*-methyl-D-aspartate receptor (NMDAR) encephalitis in patient 5. EEG example shows generalized continuous irregular 1.5- to 2-Hz spike and wave activity predominant over the anterior regions of the hemisphere and diffusely slowed background activity.

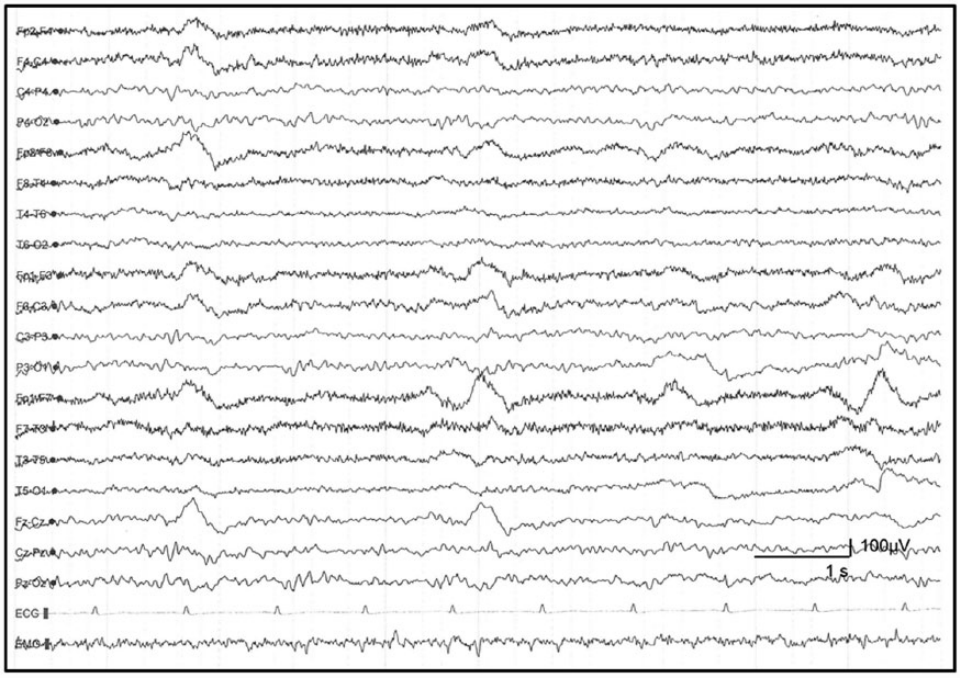

Figure 4. EEG example of patient 4 with *N*-methyl-D-aspartate receptor (NMDAR) encephalitis demonstrates frontal bursts of semirhyhtmic delta frequency activity at 1 to 1.5 Hz with superimposed beta frequency activity resembling delta brush pattern.

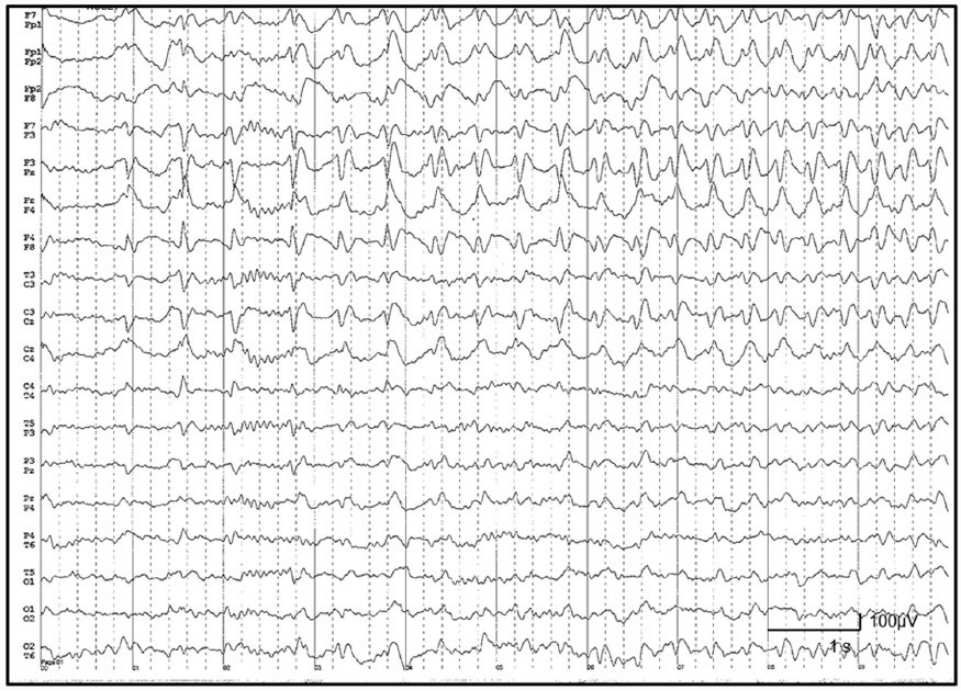

Figure 5. Subclinical seizure activity in sleep of patient 1 with anti-Hu antibody. EEG example demonstrate right frontocentral predominant 2-2.5 Hz rhythmic sharp waves which show some degree of evolution in frequency and morphology.

in atypical cases with normal MRI and CSF certain EEG findings besides clinical clues may have a guiding role in request for Ab testing.

Published studies also suggest that investigations for autoimmunity may be considered in the presence of one or more of the followings: Subacute onset of neurological symptoms (behavioral changes, somnolence, movement disorders, frequent seizures, psychosis, dysautonomia) evidence of CNS inflammation either in CSF, on imaging or on biopsy, recent or past neoplasia, history of other Ab-mediated disorders, preceding viral disease like prodromes and nonspecific white matter lesions in MRI.[3,7,10,18] Data from the current patient population further corroborate that NCSE, FIRDA, delta brush pattern, and continuous theta/delta slowing with delta paroxysms in EEG might be associated with a possible autoimmune etiology.

A notable result of our study was that epilepsy with a possible autoimmune etiology is associated with Abs directed against antigens located at the synapses (eg, GAD, amphiphysin, ion channels etc.). Among these NMDAR, GLY-R, and VGKC-complex Abs were most prevalently found in our cohort. Previous reports suggested that autoimmune limbic encephalitis associated with neuronal Abs might be an additional cause in the development of adult-onset MTLE-HS.[19] Similarly different Abs associated with a preceding viral prodrome or subacute onset encephalopathies may provoke sporadic epilepsy.[6,18,20,21] Furthermore, the presence of neuronal Abs has been shown in patients with epilepsy in whom seizures were the main presenting symptom.[6,7,22] Whether these Abs are causative or simply a marker of underlying inflammatory process needs to be still clarified.[23]

Two patients presented with classical clinical features of anti-NMDAR encephalitis; neuropsychiatric manifestations and subacute onset of seizures. Another patient was diagnosed with anti-NMDAR encephalitis after a prolonged comatose state of unknown etiology. All these cases showed FIRDA pattern in the EEG, which was reported in a few relevant EEG studies.[24,25] EEG in anti-NMDAR encephalitis often showed nonspecific abnormalities such as generalized or predominantly frontotemporal slow activity (delta-theta) in 77%, and epileptic activity in 23% of the patients.[26] There are case series of patients with anti-NMDAR encephalitis and nonconvulsive seizures, in which prolonged EEGs during status epilepticus demonstrate only rhythmic delta slowing.[27-30] Recently, a unique EEG pattern resembling the delta brush pattern of premature newborn has been identified in a series of adult patients and this finding was reported to suggest a worse outcome.[11] Although this pattern is relatively rare in the entire NMDAR encephalitis group and thus has little diagnostic value, our study suggests that it could be observed exclusively in NMDAR encephalitis (2 new cases in the current series) and thus should be carefully inquired in the differential diagnosis.

High serum anti-GAD Ab titers were detected in two of our patients with NCSE. Both of our patients presented with neuropsychiatric manifestations and showed very good response to immune-supressive and antiepileptic treatment. High titers of GAD-Ab have been associated with limbic encephalitis and

Table 3. Clinical Series of "Autoimmune" Encephalopathy or Epilepsy Associated With Neuronal Autoantibodies, Providing EEG Information.[a]

Reference (Ab Positive Sample Size)	Antineuronal Antibody	Clinical Presentation	Associated Tumor (n)	Seizure Types	Abnormal EEG Background Activity	Epileptiform Discharges/Seizures	Specific EEG Pattern
Dalmau et al (2008)[26] (100 patients)	NMDAR	Psychiatric symptoms, memory problems, seizures	58 patients	Focal, GTCS, SE, EPC	Focal (FT) or diffuse delta/theta waves	EDs	None
Irani et al (2010)[14] (44 patients)	NMDAR	Psychiatric symptoms, behavioral changes, memory problems, confusion, seizures	9 patients	Focal, generalized, focal SE	Diffuse delta/theta waves	EDs	None
Schmitt et al (2012)[11] (23 patients)	NMDAR	Behavioral changes, comatose state, seizures	11 patients	Nonconvulsive seizures (other seizure types not specified)	Focal or diffuse SWs, generalized rhythmic delta waves, fast activity	Electrographic seizures	Extreme delta brush
Viaccoz et al (2014)[40] (13 patients)	NMDAR	Psychiatric symptoms, behavioral changes, cognitive dysfunction, seizures	1 patient	Focal, GTCS, SE	Lateralized or diffuse SWs	Focal (T, TO) EDs, SE	PLEDs (T)
Irani et al (2011)[3] (29 patients)	VGKC-complex/LGI-1	Psychiatric symptoms, memory problems, confusion, dysautonomia, sleep disturbances	None	Focal, GTCS, FBDS, stimulus triggered seizures	Mild slowing, bilateral focal (FT) SWs	Focal (T) EDs, ictal activity (F, T, or FT)	None
Geschwind et al (2008)[24] (15 patients)	VGKC-complex	Behavioral changes, memory problems, seizures, myoclonus	5 patients	Not specified	Diffuse SWs	Focal (F,T, FT) EDs, ictal activity (F, FT, T)	TIRDA, FIRDA
Shin et al (2013)[41] (14 patients)	VGKC-complex/LGI-1	Behavioral changes, memory problems, seizures, dysautonomia	None	Focal, GTCS, NCSE, SE, FBDS	Focal (T) SWs, bilateral focal (T and FT) rhythmic theta/delta waves	Focal (F,T, FT,TO) EDs	PLEDs (H)
Lilleker et al (2014)[32] (6 patients)	GAD	Chronic epilepsy	None	Focal and GTCS	SWs	Focal (T, FT) EDs, ictal activity (T, FT, FC)	None
Errichiello et al (2009)[22] (6 patients)	GAD	Temporal lobe epilepsy, idiopathic generalized epilepsy	None	Focal and GTCS	Not specified	Focal (T) EDs	None
Falip et al (2012)[21] (5 patients)	GAD	Temporal lobe epilepsy	None	Focal	Not specified	Focal (T and F) EDs	None
Petit-Pedrol et al (2014)[42] (18 patients)	GABA-A GAD	Psychiatric symptoms, behavioral changes, memory problems, confusion, movement disorders, seizures, progressive hemiparesis, etc	2 patients	Focal and GTCS, SE, EPC	Diffuse SWs	Focal-multifocal EDs, ictal activity (T, FT, P, bilateral T,O,F)	GPD
Rudzinski et al (2011)[25] (28 patients)	Hu	Encephalopathy, seizures, peripheral neuropathy, ataxia, dysautonomia, movement disorder, brainstem involvement	19 patients	EPC in 2 patients, other seizure types not specified	Diffuse or focal (T and extra T) SWs	Focal (T and extra T) EDs, ictal activity (T) EPC in precentral gyrus	FIRDA, PLEDs
Holzer et al (2012)[43] (13 patients)	NMDAR GLUR-3 GAD	Psychiatric symptoms, behavioral changes, memory problems, seizures	5 patients	Focal and GTCS, SE	Diffuse theta/delta SWs	Focal (H), multifocal, generalized EDs, ictal activity (diffuse, F, H)	NCSE (T, F, bilateral FT)
Brenner et al (2013)[6] (46 patients)	VGKC complex, NMDAR, GAD, GLYR	Focal, generalized and unclassified epilepsy	None	Focal and generalized seizures	Normal or nonspecific	Focal and generalized EDs	Photosensitivity
Quek et al (2012)[5] (29 patients)	VGKC/LGI-1/CASPR-2, GAD, CRMP-5, NMDAR, Ma 2, ganglionic Ach R	Behavioral changes, cognitive dysfunction, seizures	5 patients	Focal and GTCS, EPC, myoclonic seizures	Focal (T, extra T) or diffuse SWs, fast activity	Focal (T and extra T) EDs, ictal activity (T and extra T) EPC	None
Iorio et al (2014)[39] (12 patients)	LGI1, GAD, NMDAR, Hu, unclassified Ab	Chronic epilepsy	2 patients	Focal, generalized seizures	Not specified	Focal EDs (T, FT, extra T)	None
Present study (20 patients, blinded and systematic analysis of EEGs)	NMDAR, VGKC complex, GAD, GLYR, Hu, amphiphysin	Chronic epilepsy; possible autoimmune encephalitis presented with seizures, altered mental status, psychiatric symptoms	3 patients	Focal, GTCS, NCSE, EPC	Intermittent/ continuous diffuse theta-delta waves, focal (FT) SWs, fast activity	Focal (FT, T, CP,TP), EDs, ictal activity (T, F, FT), NCSE	FIRDA, TIRDA, delta brush, PLED, bi-PLED,PED, triphasic waves

Abbreviations: Ab, antibody; EDs, epileptic discharges; SWs, slow waves; GTCS, generalized tonic clonic seizures; NCSE, nonconvulsive status epilepticus; SE, status epilepticus; EPC, epilepsia partialis continua; FBDS, faciobrachial dystonic seizures; T, temporal; F, frontal; O, occipital; C, central; H, hemispheric; P, parietal; FIRDA, frontal intermittent rhythmic delta activity; PLED, periodic lateralized epileptiform discharge; bi-PLED, bilateral, independent, periodic, lateralized epileptiform discharge; GPD, generalized periodic discharges; PED, periodic epileptiform discharge; NMDAR, *N*-methyl-D-aspartate receptor; VGKC, voltage-gated potassium channel; LGI1, leucine-rich glioma inactivated-1; CASPR-2, contactin associate protein-like 2; GLYR, glycine receptor; GAD, glutamic acid decarboxylase; CRMP-5, collapsin response-mediator protein 5; Ach R, acetylcholine receptor; GLUR-3, glutamate receptor 3; GABA-A, γ-aminobutyric acid-A.

[a]Including largest series of adult patients with EEG information based on PubMed search results.

also found in patients with epilepsy alone.[6,21,22,31,32] Only a small number of reported cases with convulsive forms of status epilepticus are associated with GAD-Ab.[33,34]

Our series included only 3 patients with paraneoplastic encephalitis with 3 different autoantibodies (anti-Hu, anti amphiphysin, and anti-NMDA-R) and therefore did not reach the power to suggesting clues indicating a cancer related disorder. Remarkably, the anti-Hu seropositive patient presented with subacute onset of drug-resistant focal seizures and in situ breast tumor 7 years after her first clinical symptoms of sensorial polyneuropathy. Seizure semiology and EEG findings suggested temporal lobe seizures. In a series of patients with anti-Hu antibodies 9% was found to have focal seizures.[35] Extratemporal EEG abnormalities were also found in 43% of anti-Hu seropositive patients suggesting an extratemporal involvement.[25] Patients with anti-ampyphysin, which is rarely associated with encephalopathy, usually present with stiff person syndrome, myoclonus, and myelopathy. In one case, this Ab was also reported to be presented with encephalopathy.[36] However, in our patient the co-incidence of diabetes causing liability for seizures has made the association ambiguous.

Table 3 summarizes some of the relevant studies reporting neuronal Abs and related EEG findings together with the present results. The high prevalence of FIRDA pattern in this study was intriguing especially because this pattern has not significantly been associated with anti-neuronal Ab positive patients. FIRDA is classically known to be related with toxic-metabolic causes as in our control group, possible association with autoimmune etiology of this pattern was also reported in a few anecdotal case reports without systematic and blind analysis on EEG.[24,25,37,38]

There are some clear limitations of this study due to its retrospective design and small sample size. The study includes a heterogeneous group of seropositive patients with a diversity of neuronal autoantibodies. Also, the correlation of EEG with clinical status over time could not be appropriately evaluated. In many of our patients, EEGs were abnormal but did not necessarily have specific and distinguishing findings that could help diagnose a possible autoimmune etiology.

Identification of possible immune-mediated mechanisms in epilepsy, status epilepticus, and other neurological symptoms is important to provide patients the benefit of immunomodulatory therapy.[5,39] Peculiar clinical presentations of these patients with autoimmune encephalitis represent the main stay of diagnosis. Certain EEG findings can provide support to an early diagnosis and appropriate treatment only in a small number of patients with epilepsy.

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Author Contributions

L Baysal-Kirac contributed to design, acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; E Tuzun contributed to conception and design, acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; E Altindag contributed to design, acquisition, analysis, and interpretation, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; E Ekizoglu contributed to design, acquisition, analysis, and interpretation, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; D Kinay contributed to design, acquisition, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; B Bilgic contributed to design, acquisition, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; P Tekturk contributed to design, acquisition, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy; B Baykan contributed to conception and design, acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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