

The psychiatric profiles of patients with temporal lobe epilepsy associated with neuronal auto-antibodies

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Abstract

Objective: Neuronal auto-antibodies (NAA) have recently been shown in some patients with chronic temporal lobe epilepsy (TLE). Psychiatric comorbidity is a significant part of the TLE course and a different profile can be a marker for “autoimmune” epilepsy. For this reason, we aimed to determine the psychiatric profiles of TLE patients associated with NAA and their differentiating features.

Methods: The sera of the included TLE patients have been tested for 8 neuronal auto-antibodies. The standardized, detailed psychiatric interviews and questionnaires (International Neuropsychiatric Interview; M.I.N.I. Turkish edition, Yale – Brown Obsessive Compulsive scale (YBOCS), The Scale for the Assessment of Positive Symptoms (SAPS)) were performed by the same researcher blindfolded to the NAA status of the patients.

Results: We evaluated 37 consecutive patients (12 male, 25 female) with TLE. NAAs had already been detected for research purposes in the sera of 20 included patients; the antibodies were found against contactin associated protein-2 (CASPR2) in 7, N-methyl-D-aspartate receptor (NMDAR) in 6, voltage-gated potassium channel complex (VGKC-complex) in 3, glycine receptor in 3 and glutamic acid decarboxylase in one patient. Social phobia was found remarkably common in the seronegative group (p:0.015). Other psychiatric symptoms did not show any difference between the seropositive and seronegative groups.

Conclusion: We could not demonstrate an alarming psychiatric profile related to NAAs in chronic TLE patients, in our small sized study. It was important to note that depression and psychosis are more frequent in patients with NAA, whereas seronegative patients displayed social phobia more frequently.

Keywords: Neuronal auto-antibodies, psychiatry, psychosis, temporal lobe epilepsy, autoimmune epilepsy

INTRODUCTION

Temporal lobe epilepsy (TLE) is the main syndrome encountered among the anti-epileptic drug-resistant chronic epilepsies (1). “Autoimmune” epilepsy has recently been established as an etiologic cause of TLE (2). Neuronal auto-antibodies (NAA) have been first found in the sera or cerebrospinal fluid of non-paraneoplastic limbic encephalitis patients who presented with seizures of temporal lobe onset and psychiatric symptoms besides other complaints with acute/subacute presentation. The causative implication of the NAA was appreciated in this particular situation especially for the neuronal surface antibodies (3, 4). Moreover, NAAs were also shown in TLE patients with a chronic TLE course besides these typical cases with limbic encephalitis (5-8).

In patients with so-called “autoimmune epilepsy”, the treatment approach may also include new options such as steroids, intravenous immunoglobulin (IVIG) etc. For this reason, it is important to recognize and screen epilepsy patients who will benefit from immune treatment modalities. Currently the clinicians do not have any markers for TLE patients who may harbor NAA, except a few clues such as status epilepticus, cognitive dysfunction and psychosis were statistically significant variables to differentiate between the VGKC-complex subgroup versus seronegative

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group in patients with mesial temporal lobe epilepsy with hippocampal sclerosis (9). Given that the prominent presenting features of autoimmune limbic encephalitis included psychiatric findings with acute/subacute onset, we hypothesized that in the chronic course of TLE associated with NAA, the psychiatric comorbidity may still be a prominent feature and may present a specific alarming profile.

On the other hand, the close relation of TLE and psychiatric conditions has been known for many decades without a clear definition of the underlying mechanisms (10). In the light of these new immunological findings, this relation needs a thorough re-evaluation. In recent literature, individual case reports and some case series showed prominent psychiatric symptoms especially depression, anxiety and psychosis in autoimmune limbic encephalitis and early and aggressive medical treatments can reduce the morbidity in these cases (11-13).

There is no systematic investigations of a series of chronic TLE patients associated with NAA with blind evaluation from a psychiatric point of view. In this study, we aimed to compare the psychiatric profiles of NAA positive TLE and NAA negative TLE groups to determine the frequency and types of psychiatric symptoms.

METHODS

Participants

This observational study was accomplished on 37 patients diagnosed with TLE by an experienced epileptologist (BB), based on their semiologic, ictal and interictal EEG and MRI findings. NAAs were sought for research purpose only in these patients with chronic course and the overall findings of our seropositive patients were already reported in two successive studies but without any systematic psychiatric analysis (5-8). Among these consecutive patients with TLE, who had the results of systematic NAA screening, those accepting our invitation to the psychiatric evaluation were enrolled in 3 successive months in 2016. The study protocol was approved by the institutional ethics committees of Istanbul Faculty of Medicine and the patients were included after their informed consent. All subjects were recruited from the Istanbul Faculty of Medicine, Neurology Department's Epilepsy Outpatient Clinics, after signing the informed consent form. The cohort was divided into two groups; 20 of them had previously found NAAs (called as the seropositive group) and as the control group 17 of them did not bear any of the investigated NAA, named as the seronegative group.

Psychiatric assessments were done in the Psychiatry Department after neurological and physical examinations by the same experienced researcher blindfolded to the NAA status of the patients.

Demographic information was collected from the patients and their medical files including age, gender, family history, past psychiatric examinations and diagnoses as well as age at onset of seizures, seizure types, MRI and EEG findings. Patients with cognitive dysfunction and with other neurological symptoms except epilepsy were not included. The following comprehensive battery was used by the blind-folded examiner.

Structured Clinical Psychiatric Interview for DSM-IV; DSM-IV covered current psychiatric complaints and current as well as life-time diagnoses. This structural examination takes nearly one hour but we examine only basic situations not the branched structures of diseases.

MINI International Neuropsychiatric Interview: This tool is designed for fast, specific, sensitive examination criteria including DSM-IV (14). We could not use MINI for DSM-V because of the lack of its validity and reliability analyses in Turkish, yet. The MINI examines general psychopathology like major depression, alcohol dependence and psychotic disorders. A limited part of MINI related to axis I and axis II disorders were left out (for DSM-IV). MINI provides convenience to examine patient samples in a short time for basic diagnoses for researches and screening.

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) are both commonly used scales for psychotic disorders for at least 30 years. SAPS contains 4 main headings (Hallucinations, Delusions, Bizarre Behavior and Positive Formal Thought Disorder) and each symptom in each of these headings were rated between 0 to 5 points. SANS is also divided to 5 domains (Affective Flattening and Blunting, Alogia, Avolition - Apathy, Anhedonia-Asociality and Attention). These two scales were used in case of the presence of a psychotic disorder diagnosed during the routine examination. Therefore we did not use these scales for all patients in this study (15).

Yale-Brown Obsessive Compulsive scale (YBOCS) is used for rating the severity of obsessive-compulsive disorder (OCD) symptoms. YBOCS is a 10-item scale; the clinician gives between 0 to 4 points for each item and total maximal rate is 40 points. (0-7: subclinical; 8-15: mild; 16-23: moderate; 24-31: severe and 32-40: extreme grades of OCD.) YBOCS was used only for patients diagnosed with OCD in the study, not for the all cases (16).

Autoantibody Testing

The sera of all included TLE patients had already been tested for NAA against voltage-gated potassium channel (VGKC)-complex antigens, contactin associated protein-2 (CASPR2), leucine-rich glioma inactivated 1 (LGI1), glutamic acid decarboxylase (GAD), N-methyl-D-Aspartate receptor (NMDAR), glycine receptor (GLY-R), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), type

A gamma amino butyric acid receptor (GABA_AR) for research purposes (8-9). Sera were kept at -80°C until assayed and cerebrospinal fluid analyses were not done due to ethical issues in these patients with chronic TLE course. Neuronal surface antibodies were detected by binding to human embryonic kidney (HEK) 293 cells transfected with plasmids containing the NR1/NR2 subunits of the NMDAR, GluR1/GluR2 subunits of the AMPAR, LGI1, CASPR2, α 1 subunit of the GLY-R and α 1/ γ 2/ β 2 subunits of the GABA_AR. Transfected cells were incubated with patients' sera (1:20) and the appropriate Alexa Fluor secondary antibody, as described earlier (6, 17-19). The binding was scored visually on a range from 0 (negative) to 4 (very strong), as previously described (18). Only scores greater than one were accepted as positive to avoid nonspecific low positivity. For detection of antibodies to uncharacterized VGKC-complex antigens, a radioimmunoassay (RIA) kit was utilized (RSR, Cardiff, UK). GAD antibodies were measured by ELISA, as per manufacturer's recommendations (Euroimmun, Luebeck, Germany). Other details of antibody testing were published previously (9).

Descriptive statistics were computed and the characteristics of the two groups of patients with and without serum NAAs were compared with non-parametric chi-square or Fisher's exact tests where appropriate. SPSS 20 software (IBM Corp.; Armonk, NY, USA) was used and the significance level was set at $p < 0.05$.

RESULTS

Study Population

A total of 37 patients (25 (67.6%) females and 12 (32.4%) males) with chronic TLE were enrolled in the study. The demographical features of the patients such as age, gender etc. were shown in Table 1, comparatively.

Brain MRI was normal in eleven patients, there were nonspecific white matter lesions in 3 patients (8.1%) and there was a cortical dysplasia in one of the patients. The brain MRI of 23 patients (62.1%) revealed mesial temporal sclerosis (MTS); right sided in 10 (27%), left sided in 10 patients (27%), with TLE and there were 3 patients (8.1%) bilateral MTS. We use concordant brain MRI and ictal and interictal electroencephalography findings besides clinical semiologic features to determine the lateralization of TLE. Accordingly, only in two patients we could not ascertain the side of TLE, whereas we determined right-sided TLE in 17 patients (45.9%) and left-sided TLE in 15 patients (40.5%). The group comparisons of the mentioned parameters were shown in Table 1.

Antibody Results

While 20 out of these 37 patients (54%) had NAA in their sera (called as seropositive group), 17 patients (46%) with TLE were seronegative and constituted the control group after completing the systematic psychiatric examination. In the

seropositive group, NAA were detected against CASPR2 in 7, NMDAR in 6, VGKC-complex in 3, glycine receptor in 3 and GAD in 1 patient. Demographical and clinical features of both groups were evaluated comparatively and we did not find any statistical significant differences for these parameters.

Psychiatric Results

The results of psychiatric interviews and formal tests were shown in Table 1. Our examination revealed that the patients who had a psychiatric problem, tend to have more than one condition, implying a complex psychiatric involvement pattern. Although, manic and hypomanic episodes, alcohol addiction, alcohol abuse, substance abuse, panic disorder, bulimia nervosa and anorexia nervosa were also interrogated in present and throughout life-time, these psychiatric conditions were found in neither seropositive nor seronegative groups. Therefore, these parameters were not shown in the Table 1. In addition, none of the patients had a history of electroconvulsive therapy.

Although there was no statistical significance for present and lifetime psychosis in group comparisons, especially psychosis during lifetime was found 3-fold increased in the seropositive group [7 patients, (35%)] in comparison to the seronegative group [2 patients, (11%)]. Distribution of various NAAs in patients with life-time psychosis showed NMDAR in 2 patients, VGKC-complex in 2 patients and CASPR2 in 5 patients. None of the particular symptoms of psychotic involvement such as hallucination type etc, showed a differential diagnostic value between the groups.

We diagnosed at least one psychotic history in 4 patients with seropositivity and 3 of them have ictal, and one of them has post-ictal psychotic experiences like auditory, tactile and Schneiderian hallucinations, bizarre behaviors (like jumping from balcony with non-suicidal thoughts) and disorganized speech. Two of seronegative patients were diagnosed with psychotic history too and one of them had disorganized speech and behaviors. Interestingly second seronegative patient had short pre- and post-ictal psychotic experiences with auditory hallucinations, murmuring and stereotypic movements like turning around her own axis. None of the symptoms of psychotic involvement such as hallucination type etc. showed a differential diagnostic value in seropositive and seronegative patients. The patients with present/acute psychosis had VGKC (n:2) and CASPR2 (n:1) antibodies in their sera.

We did not find present or life-time psychosis associated with other investigated antibodies of LGI1, AMPAR, GABAAR, GAD and GlyR. Additionally, there was no history of hospitalization to inpatient psychiatric clinics in the seronegative group. We also evaluated VGKC-complex and CASPR2 positive 7 patients together as a "K channel immunity subgroup" versus seronegative patients but we did not reveal any significant difference between these two groups for psychiatric conditions.

Table 1. Demographical, clinical and psychiatric characteristics of the subgroups with temporal lobe epilepsy

	Seropositive Patients (n:20)	Seronegative Patients (n:17)	Statistical significance
Age (y, SD)	39.34 (12.64)	35.58 (7.33)	NS
Gender (M/F)	7 (35%)/13	5 (29.41%)/12	NS
Age at onset of epilepsy	17.1 (13.92)	16.73 (9.37)	NS
Family history of epilepsy (n)	5 (25%)	4 (23.52%)	NS
MRI (n)			
Normal	6	8	
R MTS	5	5	
L MTS	6	4	NS
Bilateral MTS	3	0	
Lateralization [†]			
R TLE	7	10	
L TLE	9	6	NS
Bilateral TLE	3	0	
Politherapy	18 (90%)	11 (64.7%)	NS
Depression/present	5 (25%)	5 (29%)	NS
Depression/lifetime	7 (35%)	3 (17%)	NS
Dysthymia	7 (35%)	3 (17%)	NS
Agoraphobia	2 (10%)	0	NS
Social phobia	2 (10%)	8 (47%)	p: 0.015
GAD	0	1 (0.58%)	NS
Psychosis/ present	3 (15%) (2 VGKC, 1 CASPR2)	0	NS
Psychosis/lifetime	7 (35%) (2 NMDA, 2 VGKC, 3 CASPR2)	2 (11%)	NS
OCD	2 (10%)	3 (17%)	NS
PTSD	1 (5%)	1 (0.58%)	NS
Suicide risk	1 (5%)	2 (11%)	NS
Hospitalization ^{**}	2 (10%)	0	NS

n: number; y: year; M: male; F: female; SD: standard deviations; MRI: magnetic resonance imaging; R: right; L: left; MTS: mesial temporal sclerosis; TLE: temporal lobe epilepsy; GAD: general anxiety disorder; OCD: obsessive compulsive disorder; PTSD: post-traumatic stress disorder; NS: not significant; N-methyl-D-Aspartate receptors; VGKC: voltage-gated potassium channel complex; CASPR2: contactin associated protein-2

[†]The side of TLE could not be determined in two patients

^{**}Hospitalization to a psychiatric inpatient unit

A patient with CASPR2 autoantibodies but none of the control patients had trichotillomania, remarkably. Surprisingly, our results show that social phobia is more common in seronegative group ($p < 0.015$). Life time depression ratio is 35% and 17% for seropositive and seronegative group, respectively. We have also found same distribution and exact ratios for dysthymia.

DISCUSSION

We could not show a significantly different psychiatric involvement pattern in patients with TLE bearing various NAA. Our study disclosed that psychosis and depression were more commonly observed in TLE patients harboring these NAA. Although these differences did not reach statistical significance, our results still support the involvement of NAA in epilepsy-re-

Table 2. Neuropsychiatric profiles of seropositive patients with psychosis

n#;G	Antibody	Age	Age at onset [†]	MRI	EEG	PET	AED	Psychosis (N/LT)	Psychiatric features
1; M	NMDAR	36	20	Normal	L>R F-T sharp waves	LT hypo metabolism	LEV 2500, CBZ 800	-/+	Auditory, visual and tactile hallucinations; postictal persecutory delusions
2; F	VGKC	59	12	R MTS	R F-T sharp waves	L>R bilateral hypo metabolism	LEV 1500, CBZ 800	+/+	Schneiderian hallucinations; religiosity obsessions; obsessive guilt; repeating and checking compulsions
3; M	NMDAR	46	24	R MTS	L F-T sharp waves	L lateral T hypo metabolism	LEV 3000, TOP 400	-/+	Persecutory delusions; delusional jealousy;
4; F	CASPR2	37	20	L TLE	L F-T sharp waves	R mesial and L lateral T hypo metabolism	LEV 1500, CBZ 800, VGB 1500	-/+	Stereotyped movements and bizarre/self mutilative behaviors on the ictal period
5; F	CASPR2	31	11	B MTS	Continuous theta waves L F sharp	L F and LT hypo metabolism	OXC 900, TOP 400, LTG 500	-/+	Irritability, inappropriate affect, bizarre behaviors
6; F	CASPR2	27	21	R MTS	R>L theta waves	-	LEV 1500, CBZ 1200, TOP 150	+/+	Auditory, visual and religiosity delusions, checking compulsions
7; F	VGKC	65	1	R MTS	R F-T sharp waves	R lateral T hypo metabolism	CBZ 800, LEV 1500	+/+	Auditory and visual hallucinations

n: number; G: gender; M: male; F: female; NMDAR: N-methyl-D-Aspartate receptors; VGKC: voltage-gated potassium channel complex; CASPR2: contactin associated protein-2; MRI: magnetic resonance imaging; R: right; L: left; B: bilateral; MTS: mesial temporal sclerosis; TLE: temporal lobe epilepsy; AED: antiepileptic drug; LEV: levetiracetam; CBZ: carbamazepine; TOP: topiramate; VGB: vigabatrin; LTG: lamotrigine; OXC: oxcarbazepine; N: now; LT: lifetime; T: temporal; F: frontal
[†]year

lated psychiatric presentations. Importantly, seronegative patients in our control group with psychiatric symptoms might harbor antibodies directed against as yet unknown neuronal antigens or they might have rare antibodies not included in our screening (e.g. dopamine receptor, mGluR5 etc). We will discuss our findings regarding the established psychiatric diagnoses in the following part.

As another prominent and unexpected result of this study, social phobia was four times higher in the seronegative group in comparison to the seropositive group. The anxiety disorders are commonly seen in patients with epilepsy; the prevalence of anxiety was found between 5-20% (20, 21). Another study shows that the drug-resistant chronic epilepsy patients have the highest risk for developing anxiety disorders (22).

However, currently we do not have comprehensive knowledge for this relationship, that may relate to the unexpected nature and consequences of seizures. In the relevant

literature, association between autoimmune epilepsy and anxiety is only noted by case series (4, 23-26). In our study, we found only one patient with general anxiety disorder in the seronegative group, making an autoimmune contribution highly unlikely for the pathogenesis for this frequent comorbidity.

Social anxiety disorder is also more common in people with epilepsy compared to people without epilepsy (27). The underlying process of anxiety in epilepsy patients is probably multifactorial. To understand this process; social, psychological and neurobiological aspects should be considered all together (28). GABA is the main inhibitory neurotransmitter in the brain; it is interesting to note that antiepileptic drugs using GABAergic mechanisms also have benefits for patients with anxiety disorders (29). Insufficient control of seizures is a significant well-known predictor of anxiety (30). Our study groups had similar clinical characteristics and anti-epileptic drugs profiles were also similar. We did not observe any difference in terms of social anxiety in relation to NAA status of the TLE.

We could not explain the significant occurrence of social phobia in seronegative patients and this could be a coincidental finding in that group of patients. Patients with previously detected NAA were all invited to the study insistently, whereas we invite similar patients with seronegativity for the control group and these patients accepting our invitation to this study seem to have a specific profile. One possible explanation is that due to their social phobia, they did not consult previously a psychiatrist and in this study, they found a possibility to share their problems with a psychiatrist more easily which made them more eager to contribute.

Two seropositive and 3 seronegative patients were diagnosed with OCD. We found symmetry, violent intrusive thoughts, contamination obsessive thoughts and checking, washing and avoidant compulsive behaviors in these subjects. None of the subcategories were specific for each group of patients with NAA in these small sample.

Klein et al. determined neurological and psychiatric spectrum of 316 patients with LGI1 and CASPR2 antibodies. In this study, depression and anxiety ratio was found 16.5 %. However this study is not comparable to ours, because the patients with VGKC antibodies had various other neurological conditions not only epilepsy in the cited study (31).

Psychosis is one of the most prominent and devastating burden of the psychiatric conditions in general and particularly in patients with TLE. Besides that, psychosis is common in the autoimmune epilepsy. It was reported that mood symptoms were most common and psychosis was seen as second frequent psychiatric condition in NMDAR encephalitis (32).

When evaluating an epilepsy patient with psychosis, the temporal relation of seizure and psychiatric events should always be considered. Our systematic study showed the frequent occurrence of psychosis in relation to NAAs, without reaching statistical significance.

Mood disorders, especially depression is frequently observed in people with epilepsy. The life time prevalence of depression is between 13-20% (33). Depression and TLE were significantly associated with each other but the underlying mechanisms are not known. Accordingly to Quiske et al. the involvement of temporal lobe structures could be a possible neurobiological common denominator for developing depression in patients with TLE (34). However the lateralization of seizure focus is not significantly associated with psychiatric conditions like in our patients (35). On the other hand bipolar disease is not a common cause of psychiatric comorbidity in patients with epilepsy. Accordingly, our study did not reveal any patients with bipolar disorder. Bipolar disorders ratio was found 2.8% in chronic epilepsy but in this study both generalized and focal seizures were recruited in the same study sample (36).

In our study, the diversity of NAA is remarkable but only NMDAR, CASPR2 and uncharacterized VGKC-complex antibodies came to attention as NAAs related to psychosis. Nevertheless, our number of each NAA is not enough for comprehensive analyses, showing a weakness of our study. On the other hand, our study is the first one that evaluated patients with standardized psychiatric interview procedures performed by the same well-trained psychiatrist who did not know the NAA status.

In conclusion, consistent with previous reports mood and anxiety disorders are common causes of psychiatric comorbidity in our study for both groups. In our knowledge, this is the first study that compares psychiatric profiles of seronegative and seropositive chronic TLE patients. Even there was no statistical difference for psychosis in autoimmune epilepsy, it should be considered as a differential diagnosis for drug-resistant TLE and psychosis due to increased numbers in the seropositive group to catch the opportunity of a possible immune treatment option.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul University Istanbul School of Medicine (2012/153-937).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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