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Olgu Sunumu / Case Report

Cerebrospinal Fluid and Serum Autoantıbodıes in Drug-Resistant Temporal Lobe Epilepsıes: Case Series

Tedaviye Dirençli Temporal Lob Epilepsili Olgularda Serum ve Bos'ta Otoantikorlar: Olgu Serisi

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Abstract

We aimed to investigate the presence of neuronal antibodies in serum and cerebrospinal fluid(CSF) analysis of patients with drug resistant temporal lobe epilepsy. We evaluated 8 patients who accepted lumbar puncture with a diagnosis of drug resistant temporal lobe epilepsy. Neuronal autoantibodies were found to be negative in both serum and CSF in all patients. We investigated neuronal antibodies and clinical features in cases who were followed up for drug-resistant temporal lobe epilepsy and suspected of autoimmune epilepsy. Although neuronal antibodies were not detected in CSF and serum examinations, this may be related to the early age of onset in our study group. Autoimmune epilepsy should be considered among the differantial diagnosis with a subacute clinic, unusually high seizure frequency, variety and variability of seizures, resistance to antiseizure medications(ASMs), presence of an autoimmune disease in the person or his/her family, history of cancer or viral prodroma, demonstration of CNS inflammation and detection of neural antibodies.
Keywords: Temporal lobe epilepsy; Cerebrospinal fluid neuronal antibody; Serum neuronal antibody

Özet

Nöbet önleyici ilaca(NÖİ) dirençli temporal lob epilepsili hastaların serum ve beyin omurilik sıvısı (BOS) analizinde nöronal antikor varlığını araştırmayı amaçladık. İlaca dirençli temporal lob epilepsisi tanısı ile izlenen, lomber ponksiyonu kabul eden 8 hastayı değerlendirdik. İlaca dirençli temporal lob epilepsisi nedeniyle takip ettiğimiz ve otoimmün epilepsi şüphesi duyduğumuz olgularda nöronal antikorları ve klinik özellikleri araştırdık. Tüm hastalarda hem serum hem de BOS'ta nöronal otoantikorlar negatif bulundu. BOS ve serum incelemelerinde nöronal antikorlar saptanmasa da bu durum çalışma grubumuzda epilepsi başlangıç yaşının erken olması ile ilişkili olabilir. Subakut bir klinik, nöbet sıklığının alışılmadık derecede yüksek olması, nöbetlerin çeşitliliği ve değişkenliği, NÖİ'lara direnç, kişide veya ailesinde otoimmün hastalık varlığı, kanser öyküsü veya viral prodrom varlığı, santral sinir sistemi inflamasyonun gösterilmesi, nöral antikorların varlığında Otoimmün epilepsi ayırıcı tanıda düşünülmelidir.
Anahtar Kelimeler: Temporal lob epilepsisi; Beyin omurilik sıvısı nöronal antikoru; Serum nöronal antikor

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1. Introduction

Autoimmune encephalitis is characterized by a subacute onset clinically manifestated with various combinations as in epileptic seizures, neuropsychiatric disorders, autonomic dysfunctions and movement disorders. In addition, presence of multifocal and variable frequent seizures resistant to antiseizure medications (ASMs), comorbit autoimmune diseases, antibodies in serum and cerebrospinal fluid (CSF) samples which reflect an inflammation and radiological demonstration of the inflammation in the mesial temporal region also support the immune etiology(1,2).

Temporal lob epilepsies of an autoimmune origin generally develop on the basis of limbic encephalitis as mentioned before, the most frequently detected antibodies are: N-methyl-D-aspartate receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and gamma-aminobutyric acid receptor (GABAR) (A and B subtypes), voltage dependent potassium channel (VGKC) complex (leucine-rich glioma-activated protein 1 (LGI1) or contact-related protein 2 (CASPR-2)), glutamic acid decarboxylase (GAD) (5) and antibodies against the glycine receptor (GlyR) (2, 4). In epilepsy patients, the prevalence of neuronal autoantibodies ranges from 2.6 to 34% depending on the study design and patient selection. The essentiality of early diagnosis of an autoimmune etiology and immunotherapy poses significant importance by means of the improvement of symptoms(5).

Neuronal autoantibodies have also been demonstrated in patients with chronic epilepsy without a prior history of encephalitis who are resistant to ASMs (2, 3, 6-9). The number of studies investigating the presence of CSF neuronal autoantibodies are limited (3, 4, 10-13). Therefore, we investigated the presence of serum and CSF neuronal autoantibodies in this study to determine the presence and possible role of neuronal autoantibodies in patients with drug-resistant temporal lobe epilepsy.

2. Materials and Methods

240 patients over the age of 18 who were diagnosed with temporal lobe epilepsy and followed up for at least 1 year in our clinic were evaluated. Eight of 39 patients who followed drug resistant epilepsy, accepted lumbar puncture (LP). Patients with extratemporal lobe epilepsy who did not consent for LP, patients with contraindications for LP and less than 18 years of age were not included in the study. Patients' gender, age, age of epilepsy onset, duration of epilepsy, seizure frequency, seizure type, history (febrile seizures, trauma…etc.) including family history characteristics, comorbidities, brain Magnetic Resonance Imaging (MRI) images, Electroencephalography (EEG) findings and the number of ASMs were evaluated.

Serum and cerebrospinal fluid obtained from patients were frozen at -80°C. Presence of NMDAR, AMPAR, $GABA_BR$, LGI1, CASPR-2, GAD antibodies were looked for. ELISA method for GAD antibody and immunofluorescence method using plasmid transfected HEK293 cells for NMDAR, AMPAR, $GABA_BR$, LGI1 and CASPR2 antibodies (Euroimmun, Luebeck, Germany) were applied.

3. Results

Thirty-nine (16.25%) of 240 patients with temporal lobe epilepsy had drug-resistance. Eight patients (20.5% of resistant epilepsies) who accepted LP were included in the study. The mean age of the patients was 33.37 ± 9.07 years (minimum 20, maximum 50), the mean age of epilepsy onset was 9.22 ± 8.33 years (minimum: 4 months, maximum: 25 years). The demographic and clinical characteristics of patients are given in Figure 1.

NMDAR, AMPAR, $GABA_BR$, LGI1, CASPR-2 and GAD autoantibodies were negative in both serum and CSF of all patients.

Patient number	Gender	Age	Past medical history	Family history	Age at the onset of epilepsy (years)	Duration of epilepsy (years)	Seizure type	Seizure frequency (per month)	EEG	Antiseizure medications (mg)	MRI
1	Male	20	none	none	13	7	Focal to bilateral tonic-clonic seizures	3	Right>left fronto-temporal discharge	levetiracetam 3000, oxcarbazepine 1800, lacosamide 400, topiramate 200	Normal
2	Male	29	none	epilepsy	2	27	Focal to bilateral tonic-clonic seizures	20	bilateral temporo-parietal discharge	levetiracetam 3000, valproic acid 1500, lacosamide 400, clobazam 20	Normal
3	Male	38	febrile seizure	none	9	29	Focal seizures with impaired awareness	8	Right temporal discharge	levetiracetam 3000, carbamazepine 400, topiramate 200, lacosamide 300	Normal
4	Male	40	psychiatric comorbidity	none	0,5	39,5	Focal seizures with impaired awareness; focal to bilateral tonic-clonic seizures	4	Right fronto-temporal discharge	carbamazepine 1200, lamotrigine 400, lacosamide 300	Nonspecific T2 hyperintense lesion
5	Female	29	mental retardation, febrile seizure	epilepsy	0,3	29	Focal seizures with impaired awareness	1	Right temporo-parietal discharge	levetiracetam 2500, oxcarbazepine 600, valproic acid 1000, clonazepam 2	Normal
6	Female	30	perinatal hypoxia, meningitis	none	25	5	Focal to bilateral tonic-clonic seizures	1	Right fronto-temporal discharge	levetiracetam 3000	bilateral mesial temporal sclerosis
7	Female	31	Head trauma and operation	epilepsy	12	19	Focal seizures with impaired awareness	3	Right>left fronto-temporal discharge	levetiracetam 3000, carbamazepine 1000, zonisamide 300	right mesial temporal sclerosis
8	Female	50	Febril seizure, head trauma	none	12	38	Focal seizures with impaired awareness	5	Right temporo-parietal discharge	levetiracetam 3000, valproic acid 1500, carbamazepine 1200, clobazam 10	Nonspecific T2 hyperintense lesion

Figure 1. The demographic and clinical characteristics of patients

4. Discussion

Elisak et al. investigated the neuronal antibodies and clinical features in patients with chronic temporal lobe epilepsy. Neuronal antibodies (3 GAD, 2 CASPR-2) were detected in serum in 5% and in the CSF in 2.5% of 165 patients(11). The prevalence of GAD antibody positivity in serum was % 5.9 (3). CSF GAD antibody was examined in 11 of 15 patients with GAD antibody and 2 of them were positive (3). In another study by Höftberger et al., the 22 patients evaluated (CSF (5 patients), Serum (3 patients), CSF + serum (14 patients)) had AMPA receptor antibodies and 19/19 CSF positivity and 14/17 serum positivity(4). Antibodies were shown in all the patients whose CSF was examined. We did not detect any neuronal antibodies in CSF examinations of 8 patients who were under follow-up with a diagnosis of chronic epilepsy in this study. The low number of patients is considered to be the most important factor leading to this result.

More studies in which only serum samples were examined are present, too. Brenner et al. evaluated 416 patients diagnosed with chronic and acute epilepsy; 11% of them (chronic epilepsy 26/newly diagnosed epilepsy 20) had antibodies against (VGKC (8/12), voltage dependent calcium channel (VGCC) (0/0), GAD (4/3), NMDA-R (3/4), GLY-R (10/1), VGKC and GLY-R (1/0)) (6). Studies show that the selection of the patient group is one of the most important reasons affecting the prevalence of antibodies. We did not detect neuronal antibodies in serum examinations of the 8 patients we followed up with the diagnosis of chronic epilepsy. The results were valuable due to the fact that antibodies were studied in both serum and CSF together despite the small number of our patients. We think that evaluation of the patients in the chronic period, not involving the patients with encephalopathy and long epilepsy periods may lead to this result. It was observed in the literature that the initial findings excluding limbic encephalitis could be psychiatric complaints, psychosis, hyponatremia or tumors. These findings were detected in 64% of the patients: both onconeural and cell surface antibodies were detected at a rate of 32% and the presence of this antibody was influential in long-term outcomes (4). In this study, the researchers reported that they evaluated the CSF results as the NMDAR antibody could falsely be positive at 3% of healthy people (12). It has been reported that NMDAR antibody positivity in CSF is important for NMDAR encephalitis and immunotherapy response (10). It was seen that investigating the presence of antibodies in serum and CSF of the patients is important.

It has been reported that the late-onset TLE (mean age of epilepsy onset of 54 (19-64) years) is more common in seropositive patients (11). In another study evaluating autoimmune epilepsies, the age of seizure onset was 56.0 years (5-79) (1). Studies showing that there is no difference between seropositive and seronegative patients in terms of age epilepsy onset are also present in the literature (6, 8, 9, 14). The mean age of epilepsy onset in present study was 9.22 ± 8.33 years (minimum: 4 months, maximum: 25 years). This range may be due to the fact that different antibodies are more prominent at different ages. In addition, we think that the disease varied depending on whether it had an acute or chronic course.

There was no autoimmune comorbidity in patients with neuronal antibodies (GAD and CASPR-2) (11). Some studies showed no difference between seropositive and seronegative groups in terms of autoimmunity (8). In our patient group, no autoimmune comorbidity was present.

No history of trauma, perinatal complications and febrile convulsions were reported in the seropositive patient group in previous studies (11). 43% of the patients had precipitating factors (25% history of febrile convulsions, 7% a central nervous system (CNS) infection, 5% hypoxia, 4% head trauma and 2% other events) in the study investigating the presence of antibodies in patients with MTLE-HS (15). It has been reported in the literature that no difference exists between seropositive and seronegative groups in terms of febrile convulsion history and birth trauma (8). Risk factors (febrile convulsion, head trauma, family history of epilepsy, perinatal hypoxia and meningitis) were present in 75% of our patients. Studies indicate that the prevalence of psychotic attacks is high in the seropositive group (8, 14). One of our patients (12.5%) had a psychiatric comorbidity. It has been reported in the literature that physicians must suspect from autoimmune epilepsy in patients without risk factors for epilepsy and with seizure onsets at a late age (11). The absence of autoimmune etiology in our patients may be related to the lower age of epilepsy onset.

Nonspecific white matter changes (38.5%) were shown to be significantly higher in seropositive patients (14). In 31.25% of another group of patients with autoimmune epilepsy had normal MRI (1). While 50% of our cases had normal MRI, 25% had nonspecific T2 hyperintense lesions. NMDAR antibody screening is recommended for male patients with partial seizures, normal MRI and no clear etiology(12). MRI of 3 (75%) of our male patients was normal, 1 (25%) of our patients had nonspecific hyperintense changes and CSF NMDAR antibody results in 4 male patients were negative.

One of the limitations of our study is the lack of examination for Oligoclonal Band(OCB).

5. Conclusion

We investigated neuronal antibodies and clinical features in cases with drug-resistant temporal lobe epilepsy that we suspected an autoimmune etiology. Although neuronal antibodies were not detected in CSF and serum examinations, this result may be related to the early age of onset in our study group. Autoimmune epilepsy should be considered among the differantial diagnosis with a subacute clinic, unusually high seizure frequency, variety and variability of seizures, resistance to ASMs, presence of an autoimmune disease in the person or his or her family, history of cancer or viral prodroma, demonstration of CNS inflammation (by laboratory tests or MRI) and detection of neural antibodies (1). When neuronal antibodies are detected, immunotherapy to be applied together with ASM(s) and screening for malignancy according to the antibody will enable early treatment of patients.

REFERENCES

1. Quek AM, Britton JW, McKeon A, So E, Lennon VA, Shin C, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. *Arch Neurol*. 2012;69:582-93.
2. Vincent A, Irani SR, Lang B. The growing recognition of immunotherapy-responsive seizure disorders with autoantibodies to specific neuronal proteins. *Curr Opin Neurol* 2010;23:144-50.
3. Liimatainen S, Peltola M, Sabater L, Fallah M, Kharazmi E, Haapala AM, et al. Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. *Epilepsia*. 2010;51:760-7.
4. Höftberger R, van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, et al.

Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. *Neurology.* 2015;84:2403-12.
5. Toledano M, Britton J, McKeon A, Shin C, Lennon VA, Quek A, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. *Neurology.* 2014;82:1578-86.
6. Brenner T, Sills GJ, Hart Y, Howell S, Waters P, Brodie MJ, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. *Epilepsia.* 2013;541028-35.
7. Irani SR, Bien CG, Lang B. Autoimmune epilepsies. *Curr Opin Neurol.* 2011;24:146-53.
8. Vanli-Yavuz EN, Erdag E, Tuzun E, Ekizoglu E, Baysal-Kirac L, Ulusoy C, et al. Neuronal autoantibodies in mesial temporal lobe epilepsy with hippocampal sclerosis. *J Neurol Neurosurg Psychiatry* 2016;87:684-92.
9. Majoie HM, de Baets M, Renier W, Lang B, Vincent AJEr. Antibodies to voltage-gated potassium and calcium channels in epilepsy. *Epilepsy Res*. 2006;71:135-41.
10. Bien CG, Bien CI, Onugoren M, De Simoni D, Eigler V, Haensch CA, et al. Routine diagnostics for neural antibodies, clinical correlates, treatment and functional outcome. *J Neurol.* 2020. 267:2101-14.
11. Elisak M, Krysl D, Hanzalova J, Volna K, Bien CG, Leypoldt F, et al. The prevalence of neural antibodies in temporal lobe epilepsy and the clinical characteristics of seropositive patients. *Seizure.* 2018;63:1-6.
12. Viaccoz A, Desestret V, Ducray F, Picard G, Cavillon G, Rogemond V, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology.* 2014;82:556-63.
13. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol*. 2010;9:67-76.
14. Ekizoglu E, Tuzun E, Woodhall M, Lang B, Jacobson L, Icoz S, et al. Investigation of neuronal autoantibodies in two different focal epilepsy syndromes. *Epilepsia.* 2014;55:414-22.
15. Nóbrega-Jr AW, Gregory CP, Schlindwein-Zanini R, Neves FdS, Wolf P, Walz R, et al. Mesial temporal lobe epilepsy with hippocampal sclerosis is infrequently associated with neuronal autoantibodies. *Epilepsia.* 2018;59:e152-e6.

Ethics

Informed Consent: Consent forms were obtained from the patients and the study was approved by the Ethics Committee of Çanakkale Onsekiz Mart University (Decision No: 14-01 date: 23.07.2014).

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

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