Two limbic encephalitis cases with potassium channel antibodies

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ABSTRACT – Background: Autoimmune limbic encephalitis is presented with the involvement of limbic structures. It is a different entity rather than a component of paraneoplastic limbic encephalitis. In recent years, limbic encephalitis cases with immune-mediated voltage gated potassium channel antibody that respond to immunotherapies have been described. Case reports: We present two male patients aged 45 and 59. Both patients had elevated levels of potassium channel antibodies and presented with short-term memory impairment, psychiatric symptoms, and the first case had epileptic seizures additionally. Their radiological findings were typical for limbic encephalitis and both responded to immunotherapy. Conclusion: In this report, we emphasize that limbic encephalitis should be suspected in patients with subacute cognitive impairment, psychiatric symptoms and epilepsy resistant to therapy. Since the disorder is mostly reversible, early diagnosis and treatment is important.

Key words: autoimmune limbic encephalitis, potassium channel antibody

INTRODUCTION

Limbic structures such as mesial temporal lobe and amygdala bilaterally are involved in limbic encephalitis. Less commonly extralimbic structures such as hypothalamus and basal frontal cortex may be involved. Up to the mid-1990s, it was thought that the non-viral limbic encephalitis cases were paraneoplastic. Recently, limbic encephalitis cases with immune-mediated voltage dependent potassium channel antibodies and responsive to immunotherapy have been described.

Symptoms of limbic encephalitis are short-term memory impairment, epileptic seizures, behavior and personality alterations, confusion, irritability, depression, alterations in sleep, hallucinations and psychosis.

We present two cases that are relevant to limbic encephalitis clinically and radiologically with positive potassium channel antibodies.

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CASE REPORTS

CASE 1

Our patient was a 45-year-old right handed male working as an accountant. He was admitted with complaints of behavioral alterations, memory loss, tremor and intermittent episodes of fear for two or three months. His complaints aggravated especially in the past week. His wife defined behavioral changes of the patient as obsessive thoughts and personality features. Levetiracetam (2x1000 mg), pregabalin (1x150 mg) and valproic acid (2x250 mg) were prescribed by another physician 2 months before. His wife described two kinds of seizures, i.e. one as complex partial seizures during which the patient was staring and had oral automatisms such as lip smacking and licking, and the other type were generalized tonic clonic seizures. His wife stated that these seizures subsided upon treatment. His personal and family history was unremarkable. On neurological examination, he was conscious but disoriented in time, space and person. He had minimal ataxic tandem gait, short-term memory impairment and bizarre behavior. Mini Mental State Examination (MMSE) could not be performed because of attention deficit. Laboratory findings were normal except for hyponatremia (131 mEq/L). The patient was hospitalized with the pre-diagnosis of nonconvulsive status epilepticus or encephalitis (viral/autoimmune?). Cranial magnetic resonance imaging (MRI) was performed. Hyperintense signal changes were present in both medial temporal regions in T2 and FLAIR sections (Fig. 1 a, b, c, d).

Lumbar puncture was performed. Cerebrospinal fluid (CSF) was clear with normal pressure and without cell. Protein, glucose and other biochemical parameters of CSF were normal. CSF was investigated for herpes simplex virus (HSV) IgG, M, HSV polymerase chain reaction (PCR). CSF HSV IgG was positive, so, acyclovir treatment was also started (10 mg/kg three times a day). Acyclovir treatment was discontinued after the CSF HSV PCR was found to be negative. CSF cultures were negative. Electroencephalogram (EEG) revealed diffuse slowing (Fig. 2).

Possible autoimmune encephalitis was diagnosed with MRI and CSF findings and treatment with intravenous immunoglobulin (IVIG ) 0.4 g/kg for five days was initiated. Serum onconeural antibodies and neuronal antibody screening for limbic encephalitis were performed. For malignancy screening, thorax computed tomography (CT) and abdominal CT were performed and tumor markers were investigated. There were no findings suggestive of malignancy. NMDA receptor antibody (NMDAR ab), anti-glutamate types AMPA 1 (gl 1), anti-glutamate types AMPA 2 (gly 2), anti-CASPR 2, anti-GABA B were negative but anti LGL 1 was found positive. Onconeural antibodies for paraneoplastic study were checked; anti-hu/anna-1, anti-yo/pca-1, anti-riski/ANNA 2, anti-MA in 2/T, anti-amphiphysin and anti-CV2.1 were found to be negative. Potassium channel antibody was positive (1172 pmol/L (negative <85) (Euroimmun Laboratory, Germany). The patient’s sodium levels and serum osmolarities were low during the course of disease; Na: 123-131 Meq/L, serum osmolarity: 264-270 mOsm/L.

In the follow up, after IVIG therapy for 5 days, the patient’s clinical symptoms partially improved within 15 days. IVIG was preferred as the first choice of treatment because of the need of immediate treatment in the period when the central nervous system (CNS) infection could not have been excluded yet. After the exclusion of CNS in-
Infection and because of the inadequate response, high dose steroid was started intravenously (1000 mg/day) for 8 days and continued with oral steroids (1 mg/kg/day). Three weeks later, there was no significant difference in the lesions on MRI (Fig. 3a, b). Generalized and focal seizures were observed during hospitalization. Since the patient was already taking three antiepileptic drugs (AEDs) with inappropriate doses before admission, we regulated the doses of these drugs. Levetiracetam and valproic acid doses were increased to 3000 mg/day and 2000 mg/day, respectively. Pregabalin therapy was discontinued. Lamotrigine (with weekly 25 mg increments) 75 mg/day was added. Although he used three AEDs, his seizures responded significantly to steroid treatment. A nephrologist was consulted because of hyponatremia. Inappropriate antidiuretic hormone (ADH) syndrome was considered and fluid restriction was proposed. On the day 15 of steroid therapy, the Montreal Cognitive Assessment scale (MOCA) was performed, yielding a score of 20/30. He had mild attention deficit and short-term memory impairment, with partial improvement. The patient was discharged with oral steroid therapy and AEDs. Two months later, the level of serum potassium channel antibodies decreased significantly (286 pmol/L). This finding was consistent with the patient’s clinical response. After eight months, MOCA test was repeated and the score was 22/30. The seizures were not observed anymore and the doses of AEDs were reduced on follow up visits. He received oral steroid 1 mg/kg/day for three months and then steroid dose was gradually reduced. Significant improvement was observed in the patient’s daily activities. Follow up MRI (9 months after the first MRI) revealed disappearance of hyperintense lesions of the medial temporal regions and atrophy was observed (Fig. 4a, b, c).

CASE 2

A 59-year-old right handed male working as a curtain seller was admitted to the hospital with complaints of headache and memory impairment. The patient reported that severe headache in the frontal region had started two months before. He also complained of amnesia and occasional dizziness. He

![Fig. 2. Case 1: interictal electroencephalography revealed diffuse slowing.](image)

![Fig. 3. Follow up axial FLAIR magnetic resonance imaging (MRI; three weeks after the first MRI): there was no significant difference in the lesions (a, b).](image)
Fig. 4. Case 1: follow up magnetic resonance imaging (MRI; 9 months after the first MRI) showed disappearance of hyperintense lesions in medial temporal regions (axial FLAIR) (a, b) and atrophy (axial T1) (c).

Fig. 5. Case 2: cranial magnetic resonance imaging showed hyperintense signal changes on axial FLAIR images in the left inferior, middle and superior temporal gyrus, anterior insular cortex, inferior frontal gyrus and frontal operculum, both amygdala and the right hippocampus (a, b, c) and slightly hypointense lesions in the same regions on axial T1 images (d).

Fig. 6. Case 2: electroencephalography was normal.
had short-term memory loss, asking the same things over and over again, and thoughtfulness. Also, he was mushy, had obsessive thoughts and was crying continuously for six weeks. The patient was first evaluated at psychiatry department and escitalopram was initiated. Because of accompanying complaints, he was referred to neurology department. In his past medical history, septoplasty (in 2005) and inguinal hernia (in 2008) operation were described. His family history was unremarkable. His neurological examination was normal except for cognitive impairment. There were orientation, attention, and memory impairments. MMSE test score was 24. Laboratory findings were as follows: fasting blood sugar mildly elevated (127 mg/L), other serum biochemical parameters, complete blood count and erythrocyte sedimentation rate were normal. Cranial MRI revealed slightly hypointense lesions in T1 images and hyperintense signal changes in T2 images in the left inferior, middle and superior temporal gyrus, anterior insular cortex, inferior frontal gyrus and frontal operculum. There was no contrast enhancement and minimal diffusion restriction was observed in diffusion weighted images. T1 hypointense, T2 hyperintense signal changes were detected in both amygdala and the right hippocampus (Fig. 5 a, b, c, d).

Lumbar puncture was performed. Protein (45 mg/dL, normal range: 15-40 mg/dL), chloride and glucose levels were normal. No cell was detected in the CSF and cultures were negative. The result of herpes PCR was negative. EEG was normal (Fig. 6).

The probable diagnosis of autoimmune limbic encephalitis was considered. CSF was tested for neuronal antibodies and onconeural antibody. Then, IVIG therapy was started (0.4 g/kg for 5 days). For the purpose of malignancy screening, abdominal ultrasound, abdominal and thorax CT, tumor markers, and protein and immune electrophoresis were performed. Abdominal ultrasound revealed bladder diverticulum. Thorax and abdominal CT was normal. No changes in the lesions were observed on control MRIs. NMDA receptor antibody (NMDAR ab), anti-glutamate type AMP 1 (GL 1), anti-glutamate type AMP 2 (GL 2), anti-CASPR 2 and anti-GABA B in the CSF were negative. For paraneoplastic screening, the onconeural antibodies anti-hu/anna-1, anti-yo/pca-1, anti-risk / ANNA 2, anti-MA in 2/Ta, anti-amphiphisin and anti-CV2.1 were checked and found negative. Potassium channel antibodies were positive (103 pmol/L (negative <85) (Euroimmun Laboratory, Germany) (this result could be obtained after IVIG therapy). Herpes virus PCR in the CSF for viral encephalitis was negative. Meanwhile, because of his anxiety and depressive symptoms and insomnia, the patient had psychiatric consultation. The dose of escitalopram dose was increased (20 mg/day) and alprazolam was added to the treatment. IVIG therapy was administered for the possible diagnosis of autoimmune limbic encephalitis, however, with only minor improvement. Because of this, intravenous high dose (1000 mg/day) steroid treatment for 5 days was introduced and then continued with oral steroids (1 mg/kg/day). Because of the high level of blood glucose, insulin was started on endocrinologist’s suggestion. Follow up MOCA test score and MMSE test score were 18/30 and 23/30, respectively. Although no significant differences were observed on follow up MRI, the patient’s clinical symptoms improved significantly. The patient was followed up at the outpatient clinic after discharge from the hospital. On the last follow up visit (at 3.5 months of discharge), his memory impairment improved significantly, he could drive...
and do shopping again, his depressive symptoms decreased and his sleep was better. MOCA test score was 22/30 and MMSE test score 27/30. On follow up cranial MRI, the lesions decreased significantly, whereas hippocampal atrophy was still observed (Fig. 7 a, b, c).

DISCUSSION

We present two cases of limbic encephalitis with potassium channel antibodies, which responded to immunotherapy. In the first case, clinical presentation included behavioral abnormalities, impairment of memory and epileptic seizures lasting for 2-3 months. Similarly, the second case presented with forgetfulness, psychiatric symptoms and headache. These signs and symptoms are consistent with the clinical presentation of limbic encephalitis (1,2). Diagnostic approach is based on structural and functional imaging (MRI, PET), CSF analysis, EEG and clinical signs and symptoms in limbic encephalitis cases.

Unilateral or bilateral medial temporal hyperintensities are especially important in T2 and FLAIR sections in cranial MRI. MRI can be normal as well. Hyperintensities in extralimbic areas like frontobasal region may also be detected. Contrast enhancement of the lesions is rarely seen (1-3). Both of our two cases had T2 and FLAIR (Figs. 1 and 5) medial temporal hyperintensities. Hyperintensity in the frontobasal region was also present in our second case (Fig. 5). EEG shows unilateral or bilateral epileptic activity, focal or diffuse slowing in most cases of limbic encephalitis (3). In our first case, EEG showed generalized slowing (Fig. 2), whereas the second case had normal EEG (Fig. 6).

Some of the antibodies causing limbic encephalitis target intracellular antigens (anti-Hu, anti-CV2, anti-Ma2, anti-Ri), while others target ion channels [anti-VGKC (voltage gated potassium channel) and N-methyl-D aspartate receptor, which is associated with teratoma in young females presenting with psychiatric symptoms]. Additionally, some other antibodies are defined in a limited number of patients. However, any anti-neuronal antibodies could not be detected in 30%-40% of the limbic encephalitis cases. Since VGKC is found widely in the nervous system, patients that have antibodies against this channel may present with various clinical pictures such as neuromyotonia, Morvan's syndrome, epileptic seizures and limbic encephalitis. Most of the VGKC antibodies are LGI 1, less commonly CASPR-2 (1,2). Our first patient had significantly high levels of VGKC antibody related to LGI 1. The second patient had slight elevation. Our first patient had accompanying hyponatremia, which has been reported as an accompanying sign in limbic encephalitis cases with VGKC (2-4). Also, it has been reported that a decrease in antibody levels is related to clinical improvement after treatment, similar to our first case (5).

Pleocytosis with the predominance of lymphocytes and elevated protein levels can be detected in CSF samples of limbic encephalitis cases. However, CSF study is usually within the normal limits in limbic encephalitis cases related to VGKC antibodies (3). In our two patients, CSF investigation revealed no cells, while protein level was normal in the first patient and slightly elevated in the second patient.

Association with underlying tumor has been reported to be as low as 20%-30% in cases with VGKC antibodies (mostly lung cancer and thymoma) (2,6,7). Tumor was not detected in either of our patients.

Most of the cases with antibodies against intracellular antigens are associated with tumor and response to immunotherapy is worse. On the other hand, cases with antibodies against cell membrane surface antigens respond better to immunotherapy (2,6).

High dose intravenous followed by oral steroids, IVIG, plasma exchange (PE) and combinations (PE before IVIG) are the recommended treatment regimens. Most of the patients respond in weeks. Rituximab, cyclophosphamide or a combination of both can be tried in non-responders (if the paraneoplastic study is negative) (2). We treated our patients with IVIG as first line treatment. However, response to IVIG was insignificant in both of our patients, so we administered high dose intravenous steroid followed by oral steroid. In our first patient who was under treatment with three antiepileptic drugs seizures decreased significantly after steroid therapy, which is consistent with literature data (5).

Despite the lower level of antibody in our second case, we interpreted both cases as autoimmune limbic encephalitis with clinical picture, MRI and CSF findings, presence of neuronal antibodies and response to immunotherapy (2).

It is known that antibody mediated non-viral limbic encephalitis cases with surface membrane antibodies are reversible or have good response to treatment (8,9). In this report, we emphasize that limbic encephalitis should be suspected in patients with subacute cognitive impairment, psychiatric
Dva slučaja limbičnog encefalitisa s protutijelima kalijevih kanala

SAŽETAK – Podloga: Autoimuni limbični encefalitis očituje se zahvaćanjem limbičnih struktura. To je zaseban entitet, a ne sastavnica paraneoplastičnog limbičnog encefalitisa. Posljednjih godina opisuju se slučajevi limbičnog encefalitisa s protutijelima kalijevih kanala, koji dobro odgovaraju na imunoterapiju. Prikazi slučajeva: Prikazuju se dva slučaja muških bolesnika u dobi od 45 i 59 godina. Obojica su imali povišene razine protutijela kalijevih kanala, a bolest se očitovala poremećajem kratkotrajnog pamćenja, psihijatrijskim simptomima te u prvom slučaju i epileptičnim konvulsa. Njihovi radiološki nalazi bili su tipični za limbični encefalitis i obojica su dobro odgovorile na imunoterapiju. Zaključak: Naglašava se potreba sumnje na limbični encefalitis u bolesnika sa subakutnim kognitivnim poremećajem, psihijatrijskim simptomima i epilepsijom otpornom na terapiju. Kako je bolest uglavnom reverzibilna, od velike važnosti rana dijagnoza i liječenje.

Ključne riječi: autoimuni limbični encefalitis, protutijelo kalijevih kanala