

# Autoimmune Encephalitis: Case Reports of Anti-NMDAR and Anti-CASPR2 Encephalitides and Literature Review

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**Summary.** Autoimmune encephalitis (AE) is a group of inflammatory brain disorders involving the central nervous system (CNS) that currently includes more than 10 distinct types of the disease. Nowadays, AE has been identified as the second most frequent cause of encephalitis after infectious etiology. Over the past decade, the clinical spectrum of AE has expanded, and new clinicopathological entities are increasingly being identified. Also, our understanding of disease mechanisms and treatment strategies is rapidly evolving. In clinical practice, neuronal antibodies remain the most significant diagnostic marker currently available. Prognosis of AE varies greatly depending on the subtype and the time of immunotherapy initiation. In general, AE patients respond well to immunotherapy, therefore cognitive functions might be fully or at least partially restored. Cumulative research on the AE pathogenesis has resulted in a paradigm shift in clinical decision-making for these patients. In this article, we present two clinical cases of anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-contactin-associated protein-like 2 (anti-CASPR2) encephalitides and focus on the essential aspects of these conditions based on the latest scientific literature.

**Keywords:** autoimmune encephalitis, NMDAR, CASPR2, immunotherapy.

## INTRODUCTION

Autoimmune encephalitis (AE) is a group of inflammatory brain disorders involving the central nervous system (CNS) [1]. There are currently at least 10 different types of AE [2]. The annual incidence of encephalitis in Europe is estimated to range between 2.73 to 8.66 per 100 000 people [3]. Infectious agents account for up to 40–50% of cases, and 20–30% are attributed to autoimmune causes. The number of the remaining unexplained cases of encephalitis has declined greatly in recent years as a result of increased recognition and testing for AE [4].

AE is an immune-mediated disorder; thus, it is associated with antibodies targeting synaptic or neuronal cell surface proteins. Consequently, clinical manifestation is highly determined by the localization of the affected CNS

[1, 2]. Although AEs can be associated with oncological disorders, they must be differentiated from classical paraneoplastic syndromes (PNS). AEs are more acute in their nature and affect people of all age groups in comparison to the insidious nature of PNS [5]. AE usually presents with diverse behavioral, cognitive, autonomic, and somatic changes and poses diagnostic challenges even for experienced clinicians [1, 2]. The prognosis varies greatly depending on the subtype and the time of immunotherapy initiation. In general, AE patients respond well to immunotherapy, therefore cognitive functions might be fully or at least partially restored [2]. Recent recognition of AE in medical literature and cumulative research on the AE pathogenesis have resulted in a paradigm shift in clinical decision-making for these patients [1].

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## CASE REPORT 1

A young woman (35–40 age group) was admitted to a psychiatric hospital due to severe anxiety, impaired speech

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and gait. The patient had a history of depressive disorder and was initially treated for exacerbation of depression (the exact medical treatment was not documented). Upon admission, ataxic gait, intention tremor, dysarthria, and emotional lability were observed. A seizure lasting up to 2 minutes occurred on the 6th day of hospitalization (DOH), during this episode the patient lost consciousness, her gaze was fixated, rotational movements of the mandible and vocal component were present. A similar seizure, lasting for 7 minutes, recurred the next day. Also, magnetic resonance imaging (MRI) performed on the 6th DOH did not reveal any disease-specific changes in the brain, only signs of cerebellar atrophy were seen. On the 9th DOH, the patient was referred to a tertiary care center (TCC) for further investigation.

On examination at TCC, the patient was conscious, however, unable to explain the reason for her admission. The patient had a history of depression for the last 11 years, she was repeatedly treated for episodes of exacerbation in a psychiatric ward. Unfortunately, doctors had no information about the patient's condition prior to her initial admission to the psychiatric hospital. According to medical files she was prescribed escitalopram, lorazepam, and quetiapine. However, it was not known whether the woman followed her prescriptions correctly. In addition, she was previously diagnosed with a dissociative movement disorder. The patient did not follow all commands or answer simple questions adequately. She had intermittent fever rising to 38.3 C, other vital signs were within normal range. Her speech was slurred, with emphasis on the first syllables of the words pronounced. No motor or sensory changes were found upon examination, reflexes were symmetrical. Meningeal signs were difficult to assess due to axial muscle rigidity. Several hours later, the patient started crying, displaying emotional lability and inappropriate affect. Subsequently, the patient was unable to stand up or walk without assistance due to hypertonia in the lower limbs.

On the 13th DOH, electroencephalography (EEG) monitoring showed irregular alpha-beta activity and no pathological or epileptiform activity; the monitoring was discontinued due to inadequate patient behavior. Without confirmation of epileptic seizures and diagnosed with psychogenic nonepileptic seizures, the patient was returned to the psychiatric hospital and the previous treatment with escitalopram, lorazepam, and quetiapine was continued.

After three days (16th DOH), due to a rapid worsening of mental and somatic status (such as catatonia, episodes of hypoglycemia) and a strong suspicion of AE, the patient was referred back to TCC. At the presentation, Glasgow coma scale (GCS) was 13, her temperature rose to 38.3 C. The attending neurologist described the patient as uncommunicative. The patient was laughing involuntarily, oromandibular dyskinesias and spontaneous limb movements were present. Neurologic evaluation was not thoroughly performed due to the failure to follow commands, but hyperreflexia and clonus were noted in the legs. Meningeal signs were negative. In addition, lumbar puncture and analysis of cerebrospinal fluid (CSF) revealed an increased

protein level (0.522 g/L) and pleocytosis (55 WBC/ L), mostly lymphocytes. Polymerase chain reaction (PCR) in CSF was performed for possible bacterial and *Herpes simplex virus* (HSV) infection. In addition, CSF and blood serum were examined for the presence of AE antibodies.

Two days later (18th DOH), the patient had a fever of 40 C and the GCS score decreased to 7 (E - 2, M - 4, V - 1), she was eventually admitted to the intensive care unit (ICU) for possible sepsis. Also, diagnosis of serous meningoencephalitis or AE was included in the differential diagnosis. On the 18th DOH, laboratory tests revealed elevated C-reactive protein (CRP) (12.2 mg/L) and hyperglycemia (12.6 mmol/L). Head computed tomography (CT) showed no signs of ischemia or hemorrhages. In ICU, the patient was treated with intravenous fluid therapy, infusion of 15% mannitol 250 mg twice daily, intravenous ceftriaxone 2 grams twice daily, and intravenous acyclovir 10 mg/kg 3 times per day. Also, escitalopram 10 mg was continued and olanzapine 10 mg was added. Lorazepam and quetiapine were dismissed, carbamazepine 600 mg per day was added. An episode of tonic-clonic seizures lasting 2 minutes was successfully treated with 10 mg of intravenous diazepam. Negative CSF PCR results ruled out the possibility of neuroinfection.

On the 21st DOH, testing for neuronal antibodies in CSF was positive for anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies, and the diagnosis of anti-NMDAR encephalitis was confirmed. Brain MRI was repeatedly performed on the 26th DOH, and the findings were compatible with the diagnosis of anti-NMDAR encephalitis (Fig. 1). EEG on the 27th DOH revealed non-re-

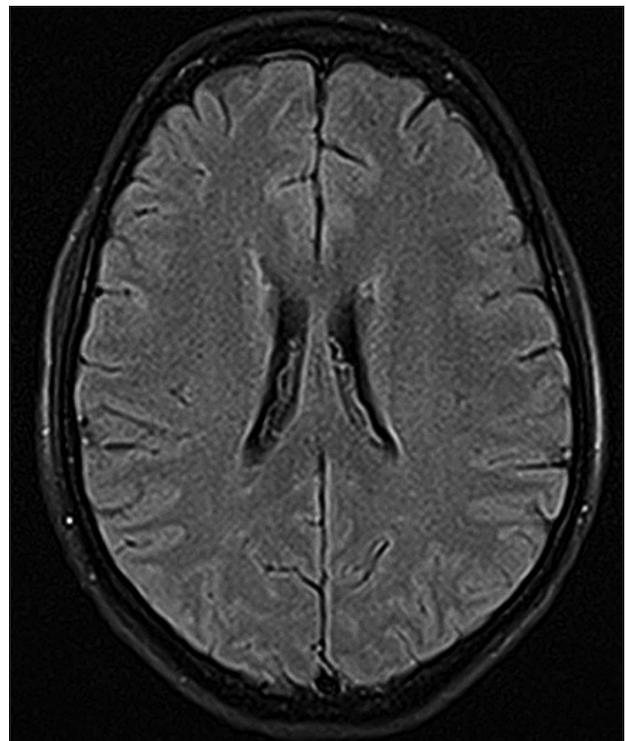


Fig. 1. MRI images of the patient with anti-NMDAR encephalitis: non-specific diffuse hyperintensity in the cerebral cortex Axial T2 Fluid attenuated inversion recovery (FLAIR) sequence.

active delta activity and possible extreme delta brush pattern in the left hemisphere. Screening for possible oncological disease with transvaginal ultrasound and abdomen/pelvis CT scan was negative.

On the 21st DOH, first-line treatment with intravenous methylprednisolone was administered (1 gram for five days followed by oral prednisolone 1 mg/kg daily, starting with 60 mg per day). On the 26th DOH, 8 sessions of plasmapheresis (performed every other day) were started. Oral prednisolone was continued and the dose was gradually lowered throughout the 26th-53rd DOH. Further dose de-escalation was as follows: 2 mg per day for the next three weeks, then the dose was reduced by 5 mg every week until full discontinuation. On the 43rd DOH, the patient was transferred from ICU to the neurology department. Carbamazepine, escitalopram, and diazepam were continued and diencephalic dysfunction symptoms (central hyperthermia, labile blood pressure, involuntary laughing and crying) were controlled by means of cooling and 10 mg of intravenous diazepam. Also, quetiapine 12.5 mg daily was added. A slight improvement in the patient's condition was obtained despite persistence of disorientation, catatonia, diencephalic dysfunction symptoms, and dyskinesias in the face.

On the 58th DOH, in pursuit of total remission, second-line immunotherapy with 700 mg of intravenous rituximab for 4 weeks was initiated. After the first week of treatment with rituximab, the patient's condition began to improve. She was reacting to attending personnel, started talking in short phrases, diencephalic dysfunction symptoms disappeared. The degree of disability on the modified Rankin Scale improved after treatment with rituximab, specifically from 5 (severe disability) to 3 (moderate disability). MMSE score after treatment was evaluated couple of times and ranged from 22 to 15, confirming mild to moderate cognitive impairment, however the MMSE did not accurately represent the patient's true functionality at the time. After finishing rituximab, on the 80th DOH maintenance immunosuppression with azathioprine 50 mg per day was initiated. The patient was unable to participate actively in rehabilitation due to cognitive deficits and was transferred to the nursing home on the 93rd DOH. In the next six months, two episodes of exacerbation occurred (after 1.5 and 3.5 months, respectively). The first relapse was treated with 4 plasmapheresis sessions and the second one was treated with two doses of 1000 mg rituximab. This decision was based on the previous suboptimal response to second-line immunotherapy. Unfortunately, the patient did not fully recover. Cognitive deficits, emotional lability, and the need for everyday assistance remained.

## CASE REPORT 2

A senior female (65–70 age group) with a history of recurrent depression was admitted to a psychiatric hospital with a recent loss of consciousness and fever episode of 39 °C.

Head CT angiography was performed, with no signs of ischemia. Lumbar puncture and CSF analysis revealed an elevated protein (0.599 g/L) and normal cytosis (1 WBC/L), no oligoclonal bands were found. The source of possible infection remained undetermined, therefore empirical antibiotic therapy was initiated. On the 10th DOH, since the diagnosis remained unclear, the patient was referred to TCC for further testing.

On examination at TCC, the patient did not have any complaints and was unable to specify the reason for her admission. Her vital signs were within normal limits. She was steadily losing muscle strength in the lower limbs in the last 3 months, and eventually needed the assistance of family members. In the last month, bladder and bowel incontinence developed, along with anorexia present for about one week. According to the medical history, the patient suffered from depression for the last 20 years. Concurrent medical conditions included primary arterial hypertension, dyslipidemia, and subclinical hypothyroidism. Neurological examination was essential for disorientation in space and time, apathy, abulia, slowed thinking, and speaking in single words with delay in answering. Mild tremor in mandible and hands, hypomimia and oral automatisms were observed. Decreased muscle strength was found in both hands and legs (distal hand muscles – 4 points, legs – 3 points). Hypertonia was determined both in upper and lower limbs. Reflexes in the upper limbs were symmetrical and absent in lower limbs. Positive pronator drift was seen in the right hand. Meningeal signs were negative. The score on the MMSE was 20, confirming mild cognitive impairment.

The same day (10th DOH), laboratory tests revealed neutrophilic leukocytosis ( $13.23 \times 10^9/L$ , neutrophils  $8.00 \times 10^9/L$ ), elevated CRP (107.2 mg/L), and hyponatremia (132 mmol/L). Due to high suspicion of AE, testing for neuronal antibodies was conducted in both serum and CSF. Anti-contactin-associated protein-like 2 (anti-CASPR2) antibodies were confirmed positive in serum. EEG findings included abnormal background activity transitioning to delta activity, pathological activity lateralisation in the right frontotemporal lobe, lowered overall brain activity, and decreased reactivity. Leukoencephalopathy and diffuse cerebral atrophy were observed on the MRI (Fig. 2). On the 12th DOH, electro-neuromyography (ENMG) revealed axonal sensorimotor polyneuropathy in lower limbs. Chest CT and abdominal ultrasound were performed to exclude PNS, and no tumor was detected.

On the 12th DOH, the patient was diagnosed with definite anti-CASPR2 encephalitis and started first-line treatment with intravenous methylprednisolone (1 gram for three days followed by oral prednisolone 1 mg/kg daily). In addition, 5 plasmapheresis sessions were performed (every other day, starting from the 15th DOH). No therapeutic response was observed after the treatment, although anti-CASPR2 antibodies were no longer detected in the following serum tests on the 26th DOH. After 4 weeks of treatment, the patient was considered an unfit candidate

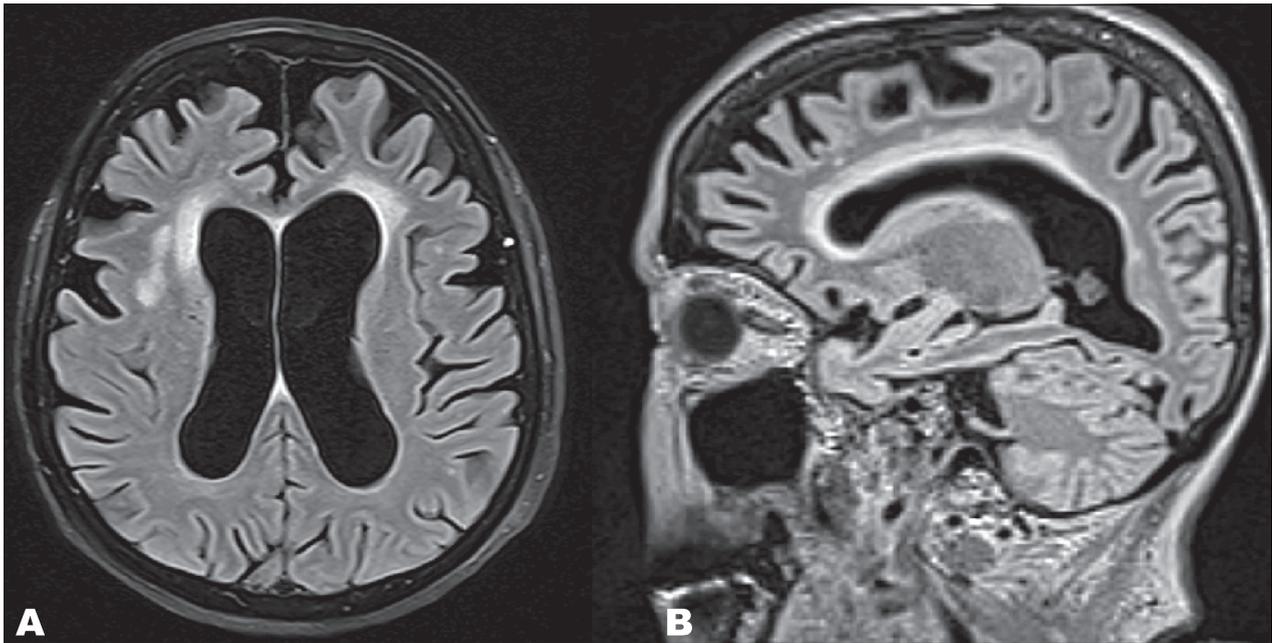


Fig. 2. MRI images of the patient with anti-CASPR2 encephalitis: leukoencephalopathy in addition to non-specific white matter lesions, diffuse cerebral atrophy, and internal hydrocephalus  
A. Axial T2 FLAIR sequence. B. Sagittal T2 FLAIR sequence.

for second-line immunotherapy with rituximab. Symptomatic treatment was continued for Parkinsonian syndrome and hypertonia. Severe cognitive impairment (MMSE score 14) and the need for constant nursing care persisted.

## LITERATURE REVIEW

### Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is an autoantibody-mediated disorder characterized by complex neuropsychiatric presentation [6]. Anti-NMDAR encephalitis, first recognized in 2007 by Dr. Josep Dalmau [7], is now known as a common cause of encephalitis among young people, with a median manifestation age of 21 years and 37% of patients being under 18 years old at the time of diagnosis [8]. The precise incidence of anti-NMDAR encephalitis remains undetermined, however, the increasing number of the cases described suggests that its incidence is higher than once assumed [9, 10]. Recent results of a systematic review by Zhang et al. are consistent with the findings of previous research, as female patients accounted for 68% of all anti-NMDAR patients and the median age was 22 years [9]. Anti-NMDAR encephalitis was once thought to be a solely paraneoplastic condition. Although this is not always the case, around one third of the patients have an ovarian teratoma (32%) [10, 11]. HSV encephalitis in another well-recognized trigger for occurrence of anti-NMDAR encephalitis [8, 12].

The NMDA receptor is a heterotetramer consisting of two GluN1 and two GluN2 subunits which are correspond-

ingly activated by glycine and glutamate [13]. The autoantibodies that characterize anti-NMDAR encephalitis primarily target the GluN1 subunit of the NMDAR (anti-GluN1 antibodies). Current evidence suggests that these antibodies can cross the blood-brain barrier and are synthesized both systemically and locally in the CNS [8]. The clinical picture can be attributed to the disturbance of the physiological functions of the NMDAR system which play a crucial role in synaptic transmission, plasticity and are important for cognition, memory, and learning [8, 14, 15]. Eventually, antibody binding leads to receptor internalization, resulting in anhedonia, depressive behavior, and memory deficit in mouse models [8, 16].

The disease usually manifests with non-specific prodromal phase followed by a sudden onset of behavior changes and altered mental status [17]. NMDAR encephalitis typically progresses over days or weeks rather than months [11]. Due to prominent neuropsychiatric symptoms, close interaction between psychiatrists and neurologists is of extreme significance for rapid clinical identification of patients with possible anti-NMDAR encephalitis [11]. Moreover, psychiatrists are often the first to encounter such patients and make pivotal clinical decisions. A multidisciplinary approach and a comprehensive understanding of psychopathology when anti-NMDAR encephalitis is suspected can ensure a successful identification of patients who would benefit from invasive diagnostic testing of the underlying cause (for example, lumbar puncture) [10, 11]. The presentation of NMDAR encephalitis is multi-staged, displaying a viral-like prodrome, usually accompanied by a mixed-mood psychosis syndrome, making it hard to distinguish from primary psychiatric illness such as schizophrenia [10]. In addition, NMDAR encephal-

litis is known for its later phase of prominent neurological symptoms such as seizures, movement disorders (like stereotypies, chorea, and dystonia), loss of consciousness, and autonomic dysfunction [9, 11]. Currently proposed diagnostic criteria for anti-NMDA receptor encephalitis are cited in the Table.

The diagnosis is generally based on compelling clinical features and is preferably confirmed by the finding of IgG anti-GluN1 antibodies in serum or CSF [10, 18]. According to Sarkis et al., antibody screening should be encouraged for any patient with “acute onset psychotic symptoms or agitation, especially if these symptoms are accompanied by catatonia, altered consciousness or flu-like prodrome” [10]. The sensitivity and specificity of IgG antibodies in CSF is high, and false positive or negative findings occur only when testing the serum [18]. It is noteworthy that the absence of antibodies in the serum or CSF is not enough to exclude the diagnosis. Changes in CSF analysis are detected in 95% of patients with anti-NMDAR encephalitis. Pleocytosis is present in around 91% of cases, increased protein in 32%, and the presence of oligoclonal bands in 67% of cases [19]. EEG is also recommended for diagnostic evaluation as it is abnormal in nearly 90% of cases of anti-NMDAR encephalitis [20]. The most common finding is generalized slowing, which is a non-specific change in brain activity [21]. When the abnormal EEG is recorded, delta range changes are reported in about a third of cases [20]. The unique EEG pattern of these patients is called extreme delta brush (EDB), described as “rhythmic delta activity at 1–3 Hz with superimposed bursts of rhythmic 20–30 Hz beta frequency activity “riding” on each delta wave” [22], much alike EDB seen in the EEG of premature neonates. Epileptiform discharges might also be present in 16% to 63% of cases [21]. On the other hand, changes in MRI imaging often reveal non-specific changes that are seen in 32.6% of cases [20]. Hyperintensity in the MRI FLAIR or T2 sequence, especially in the medial temporal lobes, and even less frequently, mild contrast enhancement can be observed [14].

As NMDAR encephalitis is a potentially lethal disease, prompt treatment is of extreme importance. First-line (corticosteroids, plasmapheresis, intravenous immunoglobulin) and second-line (such as rituximab, cyclophosphamide, mycophenolate mofetil, and azathioprine) immunotherapies, in addition to removal of tumor (if found at screening) are the key elements in the best current treatment for AE [9, 10]. Antipsychotics should be used with extreme caution in the symptomatic care of this group of patients as they may cause neuroleptic malignant syndrome or exacerbate current symptoms [10].

In patients with anti-NMDAR encephalitis, a poor prognosis resulting in neuropsychological sequelae (mainly cognitive deficits) is associated with delayed treatment, ICU admission [17, 23], and a high degree of pleocytosis in CSF [9]. Most commonly, neuropsychological dysfunction encompasses the domains of executive functions, episodic memory, and processing speed and attention [17]. In addition, for patients unresponsive to first-

Table. **Diagnostic criteria for anti-NMDAR encephalitis proposed by Graus et al. [13]**

<p><b>Probable anti-NMDAR encephalitis</b></p> <p>The diagnosis can be made when <b>all three of the following</b> criteria are met:</p> <ol style="list-style-type: none"> <li><b>Rapid onset</b> (&lt;3 months) of at least <b>four of the six following</b> major groups of symptoms (or <b>three of the following symptoms accompanied by systemic teratoma</b>): <ul style="list-style-type: none"> <li>Abnormal (psychiatric) behavior or cognitive dysfunction</li> <li>Speech dysfunction (pressured speech, verbal reduction, mutism)</li> <li>Seizures</li> <li>Movement disorder, dyskinesias, or rigidity/abnormal postures</li> <li>Decreased level of consciousness</li> <li>Autonomic dysfunction or central hypoventilation</li> </ul> </li> <li>At least <b>one of the following</b> laboratory study results: <ul style="list-style-type: none"> <li>Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)</li> <li>CSF with pleocytosis or oligoclonal bands</li> </ul> </li> <li>Reasonable <b>exclusion</b> of other disorders**</li> </ol>
<p><b>Definite anti-NMDAR encephalitis</b></p> <p>The diagnosis can be made in the presence of <b>one or more of the six major groups of symptoms</b> and <b>IgG anti-GluN1 antibodies*</b> after reasonable <b>exclusion</b> of other disorders**</p> <p>*Antibody testing should include CSF analysis. If only serum is available, confirmatory tests should be included (for example, live neurons or tissue immunohistochemistry, in addition to cell-based assay)</p> <p>**Exclusion of CNS infection, neoplasms, metabolic disorders, cerebrovascular, psychiatric disease, etc.</p>

line treatment and consequently treated with second-line immunotherapy, better clinical outcome can be expected [5]. According to cohort study performed by Titulaer et al., 81% of patients treated with immunotherapy and tumor resection (if identified) had favorable outcome after 24 months. Within 2-year period, 12% of patients had a relapse. The risk of relapse was significantly associated with not receiving second-line treatment and absence of known neoplasm [23].

### Anti-CASPR2 encephalitis

The discovery of two new antibodies in 2010 clarified the controversy surrounding voltage-gated potassium channel (VGKC) antibodies, as all previous attempts to link these antibodies to neuromyotonia (NMT, a type of peripheral nerve hyperexcitability) were unsuccessful. One of these antibodies found was anti-CASPR2. Currently, anti-CASPR2 antibodies together with antibodies against leucine-rich glioma-inactivated 1 (LG1) are used in classification of VGKC-positive cases [24–26]. Although pediatric cases have been also reported in the literature, patients are primarily male (90%) aged 60 to 70 years [25].

Furthermore, although anti-CASPR2 encephalitis is not usually associated with cancer, if present, thymoma is the most common (21.8%) neoplasm in this patient group [27].

CASPR2 is a cell adhesion protein which belongs to neurexin family [27]. This protein plays a crucial role in the normal functioning of VGKC in both the CNS and the peripheral nervous system [27]. Thus, antibodies targeting this antigen impede with normal cell adhesion between contactin-2 and CASPR2. Unlike anti-NMDAR antibodies, anti-CASPR2 antibodies do not cause internalization of CASPR2 [28].

The phenotype of patients with anti-CASPR2 is highly variable due to the involvement of both the CNS and the peripheral nervous system [25]. The most common manifestation is limbic encephalitis, followed by other presentations like Morvan syndrome (consisting of NMT, insomnia, autonomic dysfunction, and encephalopathy), cerebellar syndromes, and movement disorders. In addition, seizures, pain, weight loss, and cognitive and/or behavior alterations are also included in the clinical spectrum of anti-CASPR2 encephalitis [24, 27]. Ancillary testing can be useful for the diagnosis as pleocytosis is observed in around 28.9% of patients and MRI abnormalities are seen in 53.1% of cases [27].

Compared to anti-NMDAR encephalitis, the development of anti-CASPR2 encephalitis is relatively slow, with 30% of cases developing within one year and the median duration of the disease being 12 months, according to the systematic review of Boyko et al. [27]. Patients with anti-CASPR2 encephalitis usually respond well to immunotherapy and the disease is rarely fatal [24, 27]. Approximately 25% of patients have relapses in 6 years [25].

## DISCUSSION

The cases presented in this article highlight the importance of psychiatrists as professionals who are typically the first to encounter AE patients. Because these disorders involve changes in behavior, personality and mood, the severity of the patient's condition and the distinction between organic and psychiatric causes of the disease must be determined. Since both of the patients we presented had a history of ongoing depressive disorder, the symptoms could be attributed to an exacerbation of depression. Fortunately, in both cases, psychiatrists were able to recognize disturbing signs such as changes in consciousness, seizures, and fever, referring patients for further neurological evaluation at TCC. The time to diagnosis was about 1 and 3.5 months in the first and second cases, respectively. To our disappointment, in both cases the outcome was not favorable, as no significant improvement in neurological state and cognitive functioning was achieved. This may be partly attributed to the delayed treatment due to the insidious presentation of AE.

## Case report 1

As typically described in the literature regarding anti-NMDAR encephalitis, our patient was a 40-year-old woman. Moreover, the patient presented with classical signs attributed to anti-NMDAR encephalitis syndrome, such as psychiatric symptoms (catatonia, stupor, emotional lability, inappropriate affect, reduced speech), disorientation, seizures, dyskinesia, and autonomic dysfunction. Classical clinical symptoms, pleocytosis in CSF, possible EDB pattern in the EEG, and diffusely enhanced signal of cerebral cortex in MRI T2 FLAIR sequence contributed to the diagnosis of possible anti-NMDAR encephalitis. The definite diagnosis was made after positive anti-NMDAR antibody testing in CSF. Second-line immunotherapy was started due to an inadequate response to first-line immunotherapy, as most existing research suggests that this may enhance the patient's prognosis [23]. Unfortunately, neurological and cognitive improvement was not favorable in this case. In fact, the patient had risk factors for poor prognosis described in the literature, such as delayed ICU admission and elevated level of pleocytosis.

## Case report 2

Our patient exhibited signs that are commonly attributed to anti-CASPR2 encephalitis: subacute onset lasting several months, signs of limbic encephalitis (working memory deficit, apathy, abulia, hypomimia, slowed thinking), autonomic dysfunction (bladder and bowel incontinence), and peripheral neuropathy confirmed by ENMG. On the other hand, atypical findings such as severe brain atrophy in MRI, absence of neuronal antibodies in CSF, and medical history of the ongoing depressive disorder caused physicians doubt the diagnosis. The presence of anti-CASPR2 antibodies was confirmed only in serum samples. A tendency of higher serum sensitivity compared to that of CSF when testing for anti-CASPR2 antibodies was previously reported [26]. As previously described in the literature, patients with anti-CASPR2 encephalitis responded well to immunotherapy, however our patient was an exception. Possibly, due to the advanced stage of disease and changes in the MRI, our patient was unresponsive to first-line immunotherapy and unfit for second-line treatment with rituximab. The choice not to initiate second-line therapy was made after a careful estimation of the benefit-harm balance for this patient: severe brain atrophy, mostly in the frontotemporal regions, complete unresponsiveness to previous treatment, and possible harm of further aggressive immunosuppressive treatment were taken into consideration.

## CONCLUSIONS

Over the past decade, the clinical spectrum of AE has expanded, and new clinicopathological entities are increasingly being identified. As clinicians gain more knowledge,

AE is increasingly recognized in patients with unexplained neurological and psychiatric symptoms and signs. Any patient experiencing a sudden change in mental status should always be approached by all clinicians as a potential patient with AE. Although AE is a rare condition, neurologists working alongside psychiatrists can provide a multidisciplinary approach that can result in timely diagnosis, early treatment, and favorable patient outcomes. The presented cases describe unfavorable outcomes for patient in the absence of early treatment and can help practitioners gain a better understanding of the insidious nature of this condition.

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**AUTOIMUNINIAI ENCEFALITAI: ANTI-NMDAR  
IR ANTI-CASPR2 ENCEFALITŲ KLINIKINIAI  
ATVEJAI IR LITERATŪROS APŽVALGA**

**Santrauka**

Autoimuniniai encefalitai (AE) priskiriami centrinę nervų sistemą pažeidžiančiai uždegiminės kilmės susirgimų grupei. Iki šiol literatūroje aprašyta daugiau nei 10 skirtingų AE tipų. Naujaušiuose epidemiologiniuose tyrimuose nurodoma, kad AE yra antra pagal dažnį encefalito priežastis, nusileidžianti tik infekciniam encefalitui. Dėl gausėjančios mokslinės literatūros, per pas-

tarąjį dešimtmetį apie klinikinį AE spektrą suprantama vis daugiau. Taip pat gausėja ir sukauptų žinių apie AE atsiradimo patofiziologinius mechanizmus bei efektyvius gydymo būdus. Klinikinėje praktikoje AE antikūnų nustatymas išlieka svarbiausiu diagnostiniu žymeniu, padedančiu patvirtinti AE. Nustatyto AE tipas ir laikas nuo AE diagnozės patvirtinimo iki imunoterapijos skyrimo pradžios dažnai lemia tolimesnę sergančiojo prognozę. Dažniausiai stebimas geras atsakas į gydymą imunoterapija, o kognityvinės funkcijos gali būti sugrąžintos iš dalies ar net visiškai. AE diagnostikos ir gydymo paradigmos poslinkį lėmė tai, kad pastarąjį dešimtmetį tyrimams, susijusiems su AE, buvo skirtas itin didelis medicininės mokslinės bendruomenės dėmesys. Šiame straipsnyje pristatome du autoimuninių encefalitų atvejus, sukeltus antikūnų prieš N-metil-D-aspartato receptorių (NMDAR) ir prieš su kontaktiniu susijusį baltymą 2 (CASPR2), taip pat, remdamiesi naujausia moksline literatūra, glaustai apžvelgiame šias būkles.

**Raktažodžiai:** autoimuninis encefalitas, NMDAR, CASPR2, imunoterapija.

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