Epilepsy and Autoimmunity

Epilepsi ve Otoimmünite

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Summary

Epilepsy may present as a symptom of many neurological disorders and often an etiological factor cannot be identified. There is some evidence that immune mechanisms might play a role in the pathogenesis of certain epileptic syndromes. The evidence in support of this idea includes apparent association of seizures with certain autoimmune diseases, numerous reports of the detection of theoretically relevant serum autoantibodies, an acute or subacute onset of the seizures, a rapidly progressive course, and a favorable response to immunotherapy. In this article, we summarize (i) epilepsies where clinical and biologic data strongly support the pathogenic role of autoantibodies. (ii) epilepsies where immune-mediated inflammation occurs, but the full pathogenic cascade is either not clear or only strongly hypothesized and (iii) autoimmune diseases associated with seizures or epilepsy.

Key words: Autoantibodies; autoimmunity; epilepsy.

Özet

Epilepsi birçok nörolojik hastalıkın belirtisi olarak ortaya çıkabilir ve sıklıkla etiyolojik faktör tespit edilemez. İmmün mekanizmaların belirli epileptik sendromların patogenezinde rol oynayabileceğini dair bazı kanıtlar vardır. Belli otoimmün hastalıklar ile nöbetlerin açık bir şekilde ilişkilidi olmasına, teorik olarak uygun serum otoantikorların saptandığı çok sayıda bildirinin olması, akut ya da subakut başlangıçlı nöbetler, hızlı ilerleyici bir seyr ve immünoterapiye olumlu cevap alınması bu fikri destekleyen kanıtlardır. Bu makale, (i) epilepsilerin klinik ve biyolojik verilerinin otoantikorların patolojik rolünü kuşvetli bir şekilde desteklediğini (ii) epilepsilerde immün aracılı infiamasyonun oluşturduğu ancak tam patojenik kaskadın net olmadığını ya da sadece kuşvetli bir hipotez olduğunu ve (iii) epilepsi ya da nöbetlerle ilişkili otoimmün hastalıkları özetlemektedir.

Anahtar sözcükler: Otoantikorlar; otoimmünite; epilepsi.

The immune mechanisms may play a role in the pathogenesis of some forms of epileptic syndromes. Numerous studies have reported on the existence of a variety of immunological alterations in epileptic patients and on the observation of favourable responses of refractory epilepsy syndromes to immunomodulatory treatment. [1]

There is an association between epilepsy and certain autoimmune diseases. [2] These diseases mainly affect temporal lobes and induce limbic encephalitis or chronic temporal lobe epilepsy or involve extended brain regions causing diffuse encephalopathies presenting with seizures. [3] The autoimmune nature of some epilepsies come from the presence of autoantibodies against surface molecules of the central nervous system (CNS) cells. Although a number of different antibodies have been detected in sera of epilepsy patients, it is presumed that only antibodies directed against membrane proteins, such as ion channels and receptor proteins, have the potential to be pathogenic. [4] These antibodies may be directed to the following targets: the voltage-gated potassium channel (VGKC) complex, the α-amino-3-hydroxy-5-methyl-4-oxazolpropionic acid (AMPA) receptor, the γ-aminobutyric acid (GABA) B receptor, the N-methyl-D-aspartate (NMDA) receptor, and glycine recep-
tor. Other autoantibodies target intracellular antigens like those directed to the enzyme glutamic acid decarboxylase (GAD) and the onconeural antibodies.\[^3\]

In this article, we review some epilepsy types associated with autoantibodies and other types where immune-mediated inflammation is demonstrated but the full pathogenic cascade is not clear (e.g., Rasmussen’s encephalitis), simply presumed (West and Landau-Kleffner syndromes) or only hypothesized (hemiconvulsion-hemiplegia syndrome [HHS], fever-induced refractory epilepsy in school-aged children [FIRES] and autoimmune diseases associated with seizures or epilepsy).

Epilepsy Associated Autoantibodies Against Ion Channels and Receptor Proteins

**VGKC complex antibodies**

The VGKC complex antibodies have been identified by immunoprecipitation of VGKC Kv1 subunits solubilized in detergent from rabbit brain tissue.\[^3\] These antibodies are found in patients with acquired neuromyotonia, limbic encephalitis and much rarely in Morvan’s syndrome and mostly do not, contrary to what had been believed, bind directly to Kv1 subunits but rather to other molecules.\[^3\]

The most frequently associated molecules are leucine-rich, glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). The majority of the patients with limbic encephalitis and temporal lobe epilepsy have antibodies to LGI1.\[^6\] Typical disease onset is over 40 years of age and there is a male preponderance.\[^3\] Some patients with high titers of VGKC complex antibodies show characteristic faciobrachial dystonic seizures (FBDS) before developing temporal lobe seizures and other features of limbic encephalitis.\[^5\] In 90% of these patients the specific target autoantigen is LGI1.\[^6\] Lctal electroencephalography (EEG) abnormalities have been detected only in a small fraction of FBDS episodes, revealing contralateral rhythmic frontotemporal spikes. Magnetic resonance imaging (MRI) brain scans may show characteristic medial temporal lobe signal changes. Elevated serum VGKC antibody titers confirm the diagnosis. These seizures usually respond very well to intravenous immunoglobulin (IVIg) or corticosteroid treatments.\[^5\]

**NMDA receptor antibodies**

The clinical features are stereotyped, and include acute psychiatric disorders, amnesia and epileptic seizures that are usually of extratemporal origin. After the first stage of the disease, patients usually progress to a more severe phase with a characteristic choreoathetoid movement disorder, dysautonomia, and impaired consciousness.\[^3\] The initially reported 15 patients with autoantibodies against NMDA receptors presented with encephalitis and an underlying ovarian teratoma.\[^7\] All were young women who also had psychiatric disturbances including delusions or behavioral problems. Many further cases have been reported revealing that encephalitis appears to be commonly associated with NMDA receptor antibodies. Even though NMDA receptor antibodies are mainly observed in young women, they have also been described in children and men.\[^8,9\] The recent data show that <45% of cases are associated with tumors. Brain MRI is normal in 45%, but cerebrospinal fluid (CSF) examination reveals inflammation in >90% of cases. The EEG studies are abnormal in >90% of cases, showing asymmetrical interictal tracings. The movement disorder may also be unilateral.\[^10\] Encephalitis with NMDA receptor antibodies can be severe and even fatal, but is potentially reversible; patients may recover if the disorder is recognized and treated in time.\[^3\] Around 80% of the patients respond well to immunotherapy. IVIg, plasma exchange, and corticosteroids are the most commonly used treatments, but rituximab and cyclophosphamide have recently been advocated.\[^11\] However, there is no evidence to demonstrate that any one treatment is better than another.

**Other antibodies**

Antibodies causing limbic encephalitis and temporal lobe seizures are steadily expanding and include antibodies to GABAB receptor\[^12\] and the AMPA receptor.\[^13\] Antibodies to GABAB receptor (B1 subunit) have been reported in 15 patients presenting with refractory temporal lobe seizures as well as other symptoms of limbic dysfunction. Seven of 15 patients had tumours, five of which were small-cell lung cancer, and seven patients had non-neuronal autoantibodies. Although nine of ten patients who received immunotherapy and cancer treatment (when a tumour was found) showed neurological improvement, none of the four patients who were not similarly treated improved.\[^12\] On the other hand, patients who have limbic encephalitis with antibodies to the AMPA receptor (GluR1/2) are less likely to present with seizures. Only 3 of 10 patients had seizures as an early symptom, and one patient had seizures after a relapse.\[^13\]

Recently, glycine receptor alpha 1 antibodies have been described in adult and pediatric cases with progressive encephalomyelitis with rigidity and myoclonus. The clinical picture associated with glycine receptor alpha 1 antibodies is wider than the classical view of progressive encephalomyelitis with rigidity and myoclonus. These patients have core symptoms of muscle rigidity and spasms atypical for stiff-person syndrome. Glycine receptor antibody positive patients may also occasionally develop seizures. Treatment of patients with intravenous steroids and immunoglobulins may result in resolution of symptoms, but relapses can occur weeks later.[14,15]

Autoantibodies Targeting Intracellular Antigens

GAD antibodies
GAD is the rate-limiting enzyme for the synthesis of GABA. GAD antibodies may be found in patients with epilepsy in two different settings: acute/subacute onset of seizures accompanied by variable degrees of cognitive and psychiatric disturbance, typically in association with MRI evidence of inflammation of the mesial temporal structures (limbic encephalitis),[16] and also in patients with chronic epilepsy without clinical or MRI evidence of active CNS inflammation.[15] High serum GAD antibody levels are often associated with chronic epilepsy presenting with drug-resistant seizures.[15] The response to immunomodulatory treatments in this group has been unclear, although some positive responses have been reported.[17] The GAD antibody-positive patients had predominantly temporal lobe epilepsy and often showed serologic or clinical evidence of other autoimmune diseases.[15] High-titer GAD antibodies can rarely be found in patients with paraneoplastic limbic encephalitis and GAD antibody positive epilepsy patients may occasionally show MRI findings suggestive of limbic encephalitis.[15]

Patients with GAD antibodies are younger than those with VGKC complex antibodies. Also, GAD antibody is associated more frequently with seizures and less frequently with prominent cognitive or psychiatric disturbances.[15] Epilepsy patients with GAD antibodies also appear to be more treatment resistant than those with ion channel antibodies.[15]

Onconeural antibodies
Classical limbic encephalitis with temporal lobe seizures, amnesia, psychiatric findings or encephalomyelitis can be associated with onconeural antibodies directed against intracellular proteins Hu, Ri, Ma1/2, amphiphysin, or CV2. These antibodies are almost always accompanied by underlying tumors, but few (1-4%) can be nonparaneoplastic. Isolated epilepsy is very rarely seen in patients with onconeural antibodies and a few Hu or CV2 antibody positive patients with isolated epilepsy have been reported.[2]

Immune-Mediated Epilepsies

Rasmussen’s encephalitis
Rasmussen’s encephalitis (RE) is a rare progressive disorder of unilateral brain dysfunction.[18] It is characterized by intractable focal seizures and hemispheric brain inflammation leading to unilateral brain atrophy.[18] Patients present with progressive unilateral motor deficit and cognitive decline.[18] The cause is still unclear, although a chronic inflammation has been suggested since its first description. Although detection of antiglutamate receptor 3 (GluR3) antibodies and other antibodies (rarely NMDA receptor antibody) directed against neuronal antigens have suggested the role of humoral immunity, more recent evidence points to a cell-mediated immunity. The antibodies could presumably bind cortical neurons and thereafter induce cytotoxic T cell infiltration leading to cell death.[18-21] The main pathologic features of RE are brain inflammation dominated by T cells, microglial activation, microglial nodules and neuronal loss and astrogliosis restricted to the affected hemisphere. Infiltrating T cells have been characterized as CD8+ cells.[21] Cell death is not restricted to neurons but also affects astrocytes, thereby enhancing the neuronal loss.[22] These recent findings recall the possibility that the initiating factor in the complex pathogenesis of RE may be a viral antigen. A cytotoxic T-cell response is in fact compatible with a viral infection, and a viral infection could explain the peculiar hemispheric distribution with centrifugal expansion observed in RE.[23]

Regarding therapy, efficiency of immunosuppressive drug treatments aiming at prevention of both the destructive brain process and the refractory seizures before embarking upon large surgical resection should be determined by multicenter studies. Antiviral treatments may become a therapeutic option in the event of a proven viral cause of RE.[23]

West syndrome (infantile spasms)
West syndrome (WS) is a severe age-related epileptic encephalopathy with onset in the first year of life composed of the triad of infantile spasms, an interictal chaotic EEG pattern known as hypsarrhythmia, and mental retarda-
tion. It may occur in previously healthy children but occurs more frequently in infants with congenital or acquired neurologic problems and diseases. WS mostly benefits from adrenocorticotropic hormone (ACTH) and/or steroid treatment. Because ACTH and steroids have antinflammatory properties, a potential inflammatory or immune-mediated pathogenesis for WS has been considered. Plasma and CSF levels of cytokines have been studied in patients with WS resulting in inconclusive results. The mechanisms for WS and the role of immune and inflammatory processes might be elucidated by understanding the mechanisms by which ACTH and steroids suppress WS. These mechanisms are likely multiple and include direct effects on neuronal excitability, suppression of the levels of endogenous proconvulsant molecules such as corticotropin-releasing hormone and antiinflammatory effects.

Landau-Kleffner syndrome and continuous spike-waves during sleep

Landau-Kleffner syndrome (LKS) and continuous spike-waves during sleep (CSWS) are rare epileptic encephalopathies with typical onset in developmental age. They are characterized by aphasia, behavioral problems, and seizures. The continuous EEG epileptic activity is determined during sleep associated with neuropsychological disturbances. The LKS phenotype has been described in association with some cerebral disorders; however, in most cases no etiology can be found. A significant improvement of speech function and of autoimmune reaction during corticosteroid treatment has been observed, suggesting a pathogenic role of autoimmunity. IVlg may have a beneficial effect in this syndrome. Further support to an autoimmune pathogenic hypothesis was provided by the report of a consistent response after treatment with IVlg in a case with LKS who failed to respond to other therapies. In light of these observations, it can be concluded that autoimmune mechanisms may play role in the pathogenesis of epileptic encephalopathies including the LKS-CSWS spectrum.

Hemiconvulsion-hemiplegia syndrome

Hemiconvulsion-hemiplegia syndrome (HHS) was introduced as a syndrome in the first classification of the epilepsies reported by the International League Against Epilepsy (ILAE) in 1989 and was included among the epilepsy syndromes and epilepsies in the most recent update of the classification. This syndrome is a condition characterized by the occurrence of long-lasting unilateral convulsions in the context of a febrile illness. This is followed by a hemiplegia that starts as flaccid before becoming progressively spastic. It affects infants and young children, mainly in the first 2 years of life. The etiology and pathophysiologic mechanisms of the syndrome remain unclear; neuroradiologic studies have shown unilateral edematous swelling of the affected hemisphere at the time of initial status, followed by hemiatrophy that does not conform to any vascular territory. Most symptomatic cases complicate a preexisting brain disorder, for example, Sturge-Weber syndrome, agenesis of the corpus callosum, or tuberous sclerosis. However, some cases affect apparently healthy infants with no clinical or imaging evidence of any preexisting brain lesion, which is named as idiopathic HHS. In this subgroup, fever is the only identifiable trigger of the status epilepticus and there is neither CSF pleocytosis nor oligoclonal bands. The seizures start unilaterally with clonic jerks or head and eye deviation; they predominate on one side and may last several hours. The ictal EEG shows high amplitude 2-3 Hz rhythmic slow wave activity, mixed with low amplitude fast activity and rhythmic spikes, contralateral to the hemiconic jerks. The etiology and etiopathogenic mechanisms of this syndrome are still not fully understood.

Febrile infection-related epilepsy syndrome

Fires occurs between early childhood and the beginning of the second decade. A previously healthy child, a few days after a nonspecific febrile infection, develops focal seizures that rapidly progress to status epilepticus. The EEG between seizures shows generalized slow waves. Viral or autoimmunity tests remain negative, with a few cells in the CSF and absent oligoclonal band proteins. Early MR brain scans may show swelling of the mesial temporal structures on coronal slices in the first weeks of the disease, with an increased T2-weighted signal. The status epilepticus usually persists despite many antiepileptic drug trials. A ketogenic diet has helped in almost half of the patients. After several weeks or months, the seizures finally decrease and stop, with progressive recovery of consciousness, but patients are left with major cognitive deterioration and resistant epilepsy. Brain MRI in the chronic phase may show bilateral mesial temporal atrophy and increased T2-weighted signal, but remains normal in half of cases. Medial temporal and orbitofrontal involvements can be seen in brain positron emission tomography (PET). VGKC antibody may be positive in a few cases (LG1 and CASPR2 negative).
Autoimmune Diseases Associated with Seizures or Epilepsy

Multiple sclerosis
Multiple sclerosis (MS) is a highly common demyelinating disease that affects individuals of all ages and can result in significant neurologic disability. Although the pathogenesis of MS has not been fully defined, there is solid evidence that the development of demyelinating lesions in the white matter reflects an autoimmune process. A recent large meta-analysis of >19,000 patients revealed that seizures appear in approximately 2-5% (range 0.5-7.8%) of MS patients and often require medical therapy. Seizures may occur throughout the disease course and may be complicated by either epilepsy partialis continua or generalized tonic-clonic status epilepticus. The duration of MS symptoms prior to first seizure is generally several years. Tonic-clonic seizures account for approximately two thirds of all seizures in MS patients. Among the partial seizures, simple partial seizures are about twice as common as complex partial seizures in MS, whereas in the general population, complex partial seizures occur more frequently than simple partial seizures. Seizures are seen in patients with lesions that border the gray-white matter junction, and these lesions may exhibit gadolinium enhancement on MRI. EEG studies performed in MS patients often exhibit focal slowing, spikes, and sharp waves, but can also be normal. Sometimes a seizure is the first manifestation of the disease. Although some authors believe that seizures are more likely to occur during relapses, others have argued against it. Actually, seizures have been observed in relapsing-remitting form, as well as in secondary or primary progressive MS. In the setting of an acute relapse, seizures are benign and self-limiting and do not necessarily require treatment, whereas recurrent seizures unrelated to relapse should be treated. There are no clinical trials for treatment of epilepsy in MS patients and, therefore, no clear recommendations can be given at this time, but a systematic review of treatments is available. In pathogenesis, it has been suggested that the edema associated with active cortical lesions may be responsible for seizures in MS patients.

Systemic lupus erythematosus
Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect any part of the peripheral nervous system or CNS. CNS involvement may vary from subtle signs to severe, life-threatening conditions, and the definition of neuropsychiatric involvement is difficult due to the diffuse CNS involvement in many cases, and the lack of a satisfactory gold standard. Epilepsy is much more common in patients with SLE than would be expected. This may mean that long-term treatment with antiepileptic drugs may precipitate SLE, or that epilepsy and SLE occur together as manifestations of a genetically determined predisposition. Epileptic seizures occur more often as primary generalized seizures but they may also occur as either focal or secondary generalized tonic-clonic types. EEG shows interictal epileptic activity in all patients with recurrent epileptic seizures, however, the majority of patients with single epileptic seizures have normal interictal EEGs.

Epilepsy in patients with SLE is significantly associated with antiphospholipid (aPL) antibodies. Patients with antiphospholipid antibodies and a single epileptic seizure should be followed carefully, because of the increased risk of recurrent seizures. Epilepsy (and stroke) was more common in patients with SLE and aPL, suggesting that these antibodies exacerbate SLE, resulting in increased thrombotic and nonthrombotic brain injuries. Antibodies could lead to immune-mediated neuronal damage, which could be a pathogenic mechanism for partial epilepsy. Antibodies to transmitter receptors such as GluR3 have never been convincingly demonstrated in patients with SLE. The increased prevalence of autoantibodies is more strongly associated with epilepsy than with antiepileptic drugs, perhaps indicating that immune dysregulation may be commonly associated with epilepsy.

MRI demonstrates cerebral cortical atrophy and variable injury to the subcortical white matter seen on fluid-attenuated inversion recovery (FLAIR) sequences. There is evidence that the seizures occur in the setting of brain lesions and damage to subcortical white matter following vasculitic, inflammatory, or ischemic brain injury. Besides, the underlying systemic inflammatory cascades may be sufficient to cause seizures, or specific antibodies to neuronal antigens may trigger seizures in some patients, although the evidence is inconclusive. The development and progression of a small vessel, inflammatory vasculopathy is a hallmark of so-called “lupus cerebritis” or “lupus vasculopathy.” As blood vessels become more inflamed, there is diminution of blood flow to target areas and the development of ischemia or hemorrhage.
Large prospective studies are needed to define the role of the anticardiolipin (aCL) and anti-nuclear antibodies (ANAs) in pathophysiology of epilepsy. The presence of aPL and ANA in some patients with epilepsy has also been regarded as a consequence of anti-epileptic drug treatment.[60]

**Hashimoto’s encephalopathy**

Thyroid hormones acting via their transporters and specific nuclear receptors influence both the nervous and the immune system. The effects of these hormones on the human immune system are less well known[61] but include altered T-cell subsets and increased secretion of antibodies by thyroïd-stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH). Hashimoto’s thyroiditis is associated with auto-antibodies directed against thyroid peroxidase (TPO) or thyroglobulin (TG) associated with destruction of the thyroid follicular cells and consequent hypothyroidism. In only very rare cases,[62-64] a severe acute/subacute encephalopathy develops and is usually referred to as Hashimoto’s encephalopathy (HE). HE is broadly defined by signs and symptoms of an encephalopathy, exclusion of other causes, presence of elevated anti-thyroid antibodies and normal or mildly impaired thyroid functions. HE patients are also required to give a prominent response to immunosuppression. Acute or subacute encephalopathy is characterised with cognitive impairment, neuropsychiatric features, myoclonus, generalized tonic-clonic or partial seizures or focal neurologic deficits.[64] For the diagnosis of HE, additional requirements are exclusion of infectious, toxic, metabolic, or neoplastic processes and absence of specific antineuronal antibodies.[3]

There are no specific and diagnostic MRI findings for HE. EEG is almost always markedly altered, and seizures are present in 70-80% of patients, whereas status epilepticus occurs in 10-20%.[64] However, EEG patterns and seizure types are diverse. The clinical response to high-dose steroids is taken within days as complete or near complete. [64] More intensive and combined immunomodulatory treatment with intravenous immunoglobulins, plasma exchange, cyclophosphamide, or rituximab may be necessary in some cases.[2] The role of the antithyroid antibodies in HE is uncertain.[64] These antibodies might cause direct immune-mediated damage to the brain, but it seems equally, if not more likely, that they could be an innocent bystander or a marker for the existence of other antibodies that are directly pathogenic.

**Celiac disease**

Celiac disease (CD) is an autoimmune condition characterized by chronic inflammation in the wall of the small intestine with villous atrophy due to intolerance toward gluten, a constituent of wheat flour. The immune reaction is triggered by ingestion of gluten, a heterogeneous mixture of glutenin and gliadin that induces an abnormal immune response in predisposed subjects. Immune responses against gliadin include the activation of specific T cells, with secretion of aggressive proinflammatory cytokines that are involved in the intestinal pathology.[2] There are both humoral and cellular immune responses against tissue transglutaminase (tTG) and they are largely distributed in the CNS.

Gastrointestinal symptoms are the predominant presenting complaints in patients with CD, but it has been increasingly recognized that neurologic disorders, particularly cerebellar ataxia, peripheral neuropathy, dementia, myopathy, myelopathy, and epilepsy, are not uncommon.[67,68] In some patients, epilepsy with or without cerebral calcifications has been proposed to be one such indication of silent or latent CD. Because CD may present with malnutrition ranging from severe malabsorption to near health, nutritional deficiencies could be responsible for the development of epilepsy and other neurologic manifestations, and cerebral calcifications could result from chronic folic acid deficiency due to malabsorption. In patients with epilepsy and cerebral calcifications, it was shown that cytokines (IL-2) were taken up both in the bowel and in the occipital lobe where there were calcifications. This could be due to local inflammation or activation of glial cells, which can express IL-2 receptors.[69]

**Conclusions**

The finding of inflammatory markers and especially of autoantibodies in several epileptic disorders of unknown etiology has opened up a group of possible causes. These advances are very important for introduction of novel immunosuppressive and immunomodulatory treatments. The benefits of corticosteroids in certain epileptic encephalopathies suggest a possible role of inflammation in these syndromes. The efficacy of ketogenic diet in some epileptic encephalopathies and in severe epilepsies, reinforces this hypothesis. Nevertheless, the factors contributing to the inflammatory processes, and the clinical relevance of the biologic markers, remain largely unknown.
References


Epilepsy and Autoimmunity

45
Epilepsy and Autoimmunity


