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Autoimmune Epilepsy: New Development and Future Directions

Sandra Orozco-Suarez, Angélica Vega-Garcia, Iris Feria-Romero, Lourdes Arriaga-Pizano, Emmanuel Rodriguez-Chavez and Israel Grijalva

Abstract

In recent years, there has been accumulating evidence to support an autoimmune etiology for some patients with drug-resistant seizures, typically in the context of an antibody-mediated encephalopathy; any seizure disorder that may be caused by pathogenic autoantibodies, are an example of autoimmune epilepsy. Autoimmunity is characterized by loss of immune tolerance that causes the destruction of cells and tissues. The largest complex histocompatibility system has had a strong association with autoimmune disease, although certain genes encoding cytokines and co-stimulatory molecules increase genetic susceptibility. In spite of having scientific advances in this research area, the conditions underlying mechanisms are unknown. Goal: this chapter aims to present in synthesized form, the genetic, immunological, and environmental factors role in the autoimmunity to epilepsy, as well as the therapeutic approach that has been used to control seizures, mainly where there is a suspected anti-neuronal-antibodies circulation. Methods: a review of the work achieved during the last years in patients with this condition provides information and experience in the diagnosis and treatment of this epilepsy type. For this, a systematic search of PUBMED is conducted using the search terms “autoimmune and epilepsy, auto antibodies and epilepsy, NMDA and epilepsy, AMPA and epilepsy, and GAD and epilepsy.” The list of identified articles was complemented by additional searches for relevant articles in the reference section of the publications captured by the initial search.

Keywords: epilepsy, autoimmune encephalitis, NMDAr, immunotherapy
1. Introduction

Epilepsy is considered, as one disease with the highest prevalence of 1% population suffering from it. This pathology is defined as a cerebral disorder that is characterized by the predisposition to generate epileptic seizures, as well as the neurobiological, cognitive, psychological and social factors associated with this condition [1]. There is evidence that specific neuronal auto antibodies with pathogenic potential may be present in a subset of patients with epilepsy. Importantly, it has recently been shown that some patients with these serum auto antibodies and mainly in CSF are often refractory to treatment with standard antiepileptic drugs (AEDs) and, on the other hand, may respond well to immunomodulatory therapies. In this way, it has been possible to make a therapeutic approach. The autoimmune basis led to the introduction of immunotherapy (IT) in some drug-resistant syndromes [2], prompted by an intensive search for self-antibodies (Abs) in epilepsy. The findings of limbic encephalitis associated with self- Abs against neuronal plasma membrane (receptors, ion channels) and intracellular proteins have further fueled this search. As seizures are key to the infestation manifest, this disorder serves as a model for understanding epilepsy-immune system interaction [3], evoking the possibility that said antibodies could cause patients with epilepsy alone, and leading to the search for self-Abs in patients with pharmaco-resistant epilepsy (PE). Recent prospective study found neuronal auto-Abs in about 10% of pediatric patients with seizures, a rate twice as high as in controls with other systemic diseases; this creates a quandary for clinicians as to when treatment should be chosen in pharmaco-resistant epilepsy patients [4].

2. Genetic and clinical heterogeneity of epilepsy

Autoimmune conditions are the result of multifactorial processes involving dysregulation of both the innate and adaptive immune system, and the possession of predisposing gene alleles, which ultimately at a certain moment in time “trigger” a sustained loss of self-tolerance resulting in an immune-mediated damage of autologous tissues [5]. The innate immune response is the host’s first line of defense against invading microorganisms, while the adaptive immune response is the injection in a time-delayed but antigen-specific manner. Adaptive immune responses are driven by specific components of bacteria or antigen, require several days to develop, and exhibit immunological memory for a lifetime, such that a second exposure to the same antigen results in an accelerated and specific response. Cell populations of the innate immune system, such as dendritic cells (DCs), which are antigen-presenting cells, promote primary T cells and B cell responses and therefore relate innate and adaptive immunity [6]. T cells that are reactive to self-antigens are largely deleted in the thymus in an active process termed thymic or central tolerance induction. Central tolerance induction occurs in both the immature thymus T cells and bone marrow for B cells. During the ontogeny of lymphocytes, T lymphocytes receptors (TCRs) that recognize high affinity, self-peptides exposed in The HLA molecules are deleted by clonal deletion, in order to avoid self-reactive clones. Only the clones whose TCRs recognize their own peptides with medium affinity, mature in secondary lymphoid organs. This shows that the HLA molecules themselves determine the TCR
repertoire. Peripheral tolerance mechanisms include clonal anergy (absence of co-stimulatory molecules), unawareness and suppression by the activation of CD4^+ CD25^+ FOXP3^+ regulatory T cells. In the antigen recognition, the segments α1 and β1 of the HLA molecules (both polymorphic), the processed peptide and the TCR are involved [7]. In fact, some processed peptides are only exposed in certain HLA molecules. So the molecules of the HLA itself also determine which peptide can be recognized by the mature T lymphocytes TCR. The HLA molecules of an individual, determine their immune response at two levels: during negative selection in the thymus and in the selection of peptides at the periphery [7, 8]. By the other way, the new lines of AEs research focused on the genes coding for molecules involved in the central tolerance and peripheral induction. These genes found on any chromosome encode for proteins involved in the lymphocytes and molecules selection, acting as death receptors or co-stimulatory molecules. Most AEs caused the difficulty in knowing the triggering agents. The AEs caused by a mutation in a single gene (monogenic), which are small, provide clinical and experimental evidence of the contribution of different control mechanisms of self-reactivity [9].

2.1. Genetic diagnostics of epilepsies

In epilepsy, there are no studies associating autoimmunity with genetic factors; however, studies have focused on other autoimmune diseases and focuses are mainly associated with major histocompatibility system. Several alleles of classical human leukocyte antigen (HLA) genes in the MHC locus have been linked to autoimmune diseases. The genes coding for HLA molecules are located on the short arm of chromosome 6 in the region of the major histocompatibility complex (MHC). The HLA-I genes encoded by the HLA-A, B, C, E, F, and G genes are expressed in all the genes encoding the class I, II, and III molecules. The nucleated cells and the platelets and HLA-II molecules are products of the HLA-DP, DQ, DR, DM, DO genes and are constitutively expressed in B lymphocytes, monocytes, macrophages, dendritic cells, endothelial cells, intestinal epithelial cells, cells early hematopoietic and activated T lymphocytes. The class III region called HLA non-classical contains a collection of approximately 20 genes. This region includes those encoding complement proteins, components involved in the intracellular processing of peptides (TAP1, TAP2) and epithelial cell surface molecules (MICA-MICB) [10, 11]. The fundamental function of molecules HLA-I and HLA-II is to bind their own and foreign peptides in order to transport them to the cell membrane. Once exposed, they are recognized by the TCR, so they have a central role in the execution of the immune response. HLA-I molecules primarily present cytosolic (such as a viral or tumor) peptides to CD8+ cytotoxic T cells, whereas HLA class II molecules generally have extracellular peptides (such as bacterial) to CD4+ helper T lymphocytes. This functional division of peptide presentation ensures the activation of T cells (CD8+ and CD4+) and therefore the appropriate immune response for each type of antigen [10]. The HLA system has two fundamental properties that make it difficult to understand, the genes involved in the predisposition to AEs: polymorphism and linkage disequilibrium (LD) [12]. I-II molecules are the most polymorphic of the whole genome. This property determines that for each loci, there are multiple alleles whose DNA sequences only differ by a few nucleotides. These local mutations are known as single nucleotide polymorphism (NSP). Genes located in the MHC region have a
high genetic association. This property is known as linkage disequilibrium (LD) and describes the tendency of certain genes to inherit together given their closeness. The above determines that the frequency of these genes (in a single haplotype) in the population is greater than their individual inheritance [13, 14]. Inside the AEs gene, the greatest association is with the molecules of the HLA. The siblings concordance with identical HLA is 15% compared to 1% for siblings with a non-identical HLA. This figure is indicative of the strong association between HLA molecules and a risk to develop an autoimmune disease. In some diseases, this association is stronger as in ankylosing spondylitis (AS), while in others, it is weaker than in the myasthenia gravis (MG) [15].

Genetic study with a cohort of 24 cases of Rasmussen (RE) autoimmune encephalitis, the human leukocyte antigen (HLA) class I and class II genes were sequenced; they got the association of three C*07 alleles: 02:01:01, DQA1*04:01:01, and DQB1*04:02:01, that increased the relative risk of RE. It has been shown that HLA-B*07:02 is a risk factor for Graves’ disease. In addition, 33% of patients in that study had HLA-A*03:01:01, DQA1*, 05*01:01:01, DQB1*02:01:01 and 20% patients showed a combination of HLA alleles (DQA1*01:02:01:01, DQB1*06:02:01, DRB1*15:01:01:01), that have been linked to the risk of developing multiple sclerosis [15].

The same way, anti-leucine-rich glioma-inactivated (LGI1) encephalitis was associated [16] with the DRB1*07:01-DQB1*02:02 haplotype (10 patients, 91%) in HLA class II genes, as well as with B*44:03 (8 patients, 73%) and C*07:06 (7 patients, 64%) in the HLA class I region. The prevalence of these alleles in anti-LGI1 encephalitis was significantly higher than that in the epilepsy controls or healthy controls. By contrast, anti-NMDAR encephalitis was not associated with HLA genotypes. Additional analysis using HLA-peptide binding prediction algorithms and computational docking underpinned the close relationship; this finding suggests that most anti-LGI1 encephalitis develop in a population with specific HLA subtypes [17].

2.2. Influence of environmental factors

The concordance values between monozygotic twins are indicative of the role of environmental factors in the development of autoimmunity. Within this group are infections (viruses, parasites, bacteria, and fungi), hormones and immune system regulation loss. The action mechanism proposed for these factors is based on the release of pro-inflammatory substances inducing the danger signals expression and the consequent activation of auto-reactive T lymphocyte clones.

T cell TCRs recognize different peptides in the groove of the HLA molecule as long as they maintain the same charge distribution and spatial orientation. Hence, own and foreign molecules that have this similarity are recognized by lymphocytes and produce an immune response [18]. The creation of an inflammatory microenvironment increases the presence of antigens due to tissue damage and the expression of co-stimulatory molecules. In this medium, the anergized T lymphocytes may activate and stimulate the immune response against antigens themselves [19].
Nevertheless, infections can also modify the clinical manifestations associated with autoimmune epilepsy (AE) in such a way that infections are involved in the induction and protection of AEs in genetically predisposed individuals. This dual role underlying mechanism compression offers new ways of controlling and treating these diseases [20].

3. Conventional etiological mechanisms of neural proteins as antibodies

The target antigens that play a critical role in neuronal transmission and in plasticity include the N-methyl-D-aspartate (NMDA) receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), the gamma-aminobutyric acid receptor (GABA), the glioma-inactivating leucine-rich protein (LGI1) and the contacting-associated protein 2 (CASPR2), a protein that plays a key role in the normal function of voltage-dependent potassium channels [21].

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The structure of NMDA receptors (R-NMDA) are formed by combinations of different subunits: NMDAR1 (NR1), NMDAR2 (NR2), and NMDAR3 (NR3); which form a Ca++ permeable ion channel. A single gene encodes the NR1 subunit; however, transcription can generate at least eight isoforms, whereas for NR2-type subunits there are four different genes encoding NR2A, NR2B, NR2C, and NR2D subunits. Functional NMDA receptors are composed of heterotetramers, and formed by two dimers twisted by the subunits NR1-NR2, where in the NR1 subunit it possesses a glycine binding site and each in the NR2 subunit, a glutamate binding site, with two binding sites for glycine (S1) and two for glutamate (S2) in each receptor. The NR1-NR2 dimer is considered the basic functional structure at each receptor, where different physiological and pharmacological binding sites are found for different ligands [22, 23]. Each ionotropic receptor subunit has similar molecular structure, which is organized into four functional domains, which are: an extracellular domain with the amino (N) terminal (DNT), a ligand binding domain (DBL), a region (M1–M4), where the M2 segment that partially enters the membrane forms the ion channel, and finally, a carboxyl domain (C) in the intracellular region (DCT) (Figure 1(A)) [24, 25].

In NMDARAS, IgG antibodies are directed to the N-terminal extracellular domain of the GluN1 subunit of the NMDA receptor (Figure 1), specifically an epitope region at GluN1 aa369 [26–28]; the cultures of dissociated rat hippocampal neurons and antibody-containing cerebrospinal fluid (CSF) from patients with NMDARAS have been used to study the molecular mechanism by which IgG antibodies cause hypo function of the NMDAR [29]; antibodies decrease the levels of synaptic NMDA receptor and disrupt NMDA receptor currents in cultured neurons. In addition, antibodies disrupt the interaction between NMDAR and the ephrin B2 receptor (EphB2R), a major stabilizer of NMDARs at postsynaptic sites, facilitating the displacement of NMDARs from the synapse [29]. The antibody does not act as a receptor antagonist, by modulating the physiological receptor binding domain, but causes capping and internalization of the receptor [30]. Antibody-mediated internalization is independent of NMDAR activity and does not occur as a compensatory response to the agonism of the receptor, suggesting that the mechanism of internalization is primarily NMDAR cross-linking by patient antibodies [29].
Encephalitis associated with antibodies against GABAB1 receptor is generally presented as limbic encephalitis, as well as drug-refractory seizures. In a series of 15 patients, the mean age of presentation was 62 years (range 24–75) and both sexes were similarly affected. About half of the patients had an associated tumor, either a small cell lung carcinoma or a neuroendocrine lung tumor. These patients usually have antibodies to various non-neuronal proteins of uncertain significance, which suggests a susceptibility to autoimmunity [30].

In the knockout mice to the GABAB1 receptor, a variety of neurological and behavioral alterations are found, including spontaneous seizures, increased anxiety, hyperactivity, hyperalgesia and memory impairment, suggesting a dysfunction of the limbic system [31, 32].

In contrast, patients present with limbic encephalitis in conjunction with antibodies to the AMPAR were not present with seizures as frequently: only 3/10 had seizures as presenting feature with one other patient having seizures after a relapse [33].

Figure 1. (A) Structure of AMPA receptor subunits. The transmembrane topology is shown, along with the flip/flop alternatively spliced exon, and the two ligand-binding domains (S1 and S2). Glycosylation sites are shown as trees in the N-terminal region; this region is associated with immune response. (B) Flow cytometry demonstrates the presence of T lymphocytes of the CD8+ class with greater activation, as well as B lymphocytes; here it can be known that the immune process has extravasated to the cerebral parenchyma. (C), (D) and (E) the tissue based assay. Mouse brain tissue sections, such as hippocampus are stained with the patient’s serum or CSF by indirect immunoperoxidase technique. (E) Shows CSF immunoreaction at the hippocampus level of the cytoplasmic and a neuronal surface in D (anti-human IgG-Px, Abcam-ab97225). (F) TBA in F, shown a reaction at neuronal surface level that colocalizes with GAD65/67 (Alexafluor 546, Invitrogen Molecular probes). (G) Immunoblot, CSF recognizes 100 and 50 Kd proteins (Anti-human IgG-Px, Abcam- ab97225).
Besides, anti-AMPA-GluR3B antibodies have been associated with many pathological effects: they activate glutamate, AMPA receptors, and are involved in the processes of “excitotoxicity.” The phenomenon is associated with various pathological states of the CNS including: epilepsy, hypoxia/ischemia, and trauma. In animal and in vitro models, anti-NMDA-NR1 antibodies may be highly pathogenic, as they may cause a decrease in surface NMDA receptors expressed in hippocampal neurons, and also decrease the density and synaptic localization of receptors NMDA. The expression of these NR1a subunits correlates with the distribution of high-affinity NMDA receptors by agonists. Anti-NMDA-NR1 antibodies induces reduction in expression through cross-linking and internalization of NMDA receptors. Such changes may impair glutamate signaling through NMDA receptors and lead to various abnormal neuronal/behavioral/cognitive/psychiatric disorders.

Nevertheless, anti-AMPA-GluR3B antibodies induce many pathological effects that activate glutamate/AMPA receptors, which are involved in excitotoxic damage, the complement activation is modulated by regulatory proteins in which the activation plays a central role in the pathogenesis of brain damage and induces behavior and motor impairments. It has been observed in animal and in vitro models that anti-NMDA-NR1 antibodies can be highly pathogenic, as they may cause a decrease in surface NMDA receptors expressed in hippocampal neurons, and the density and synaptic localization of NMDA, probably by the internalization of receptors, which can impair glutamate signaling through NMDA receptors and lead to various neuronal/behavior/cognitive/psychiatric alterations. Knock-out mice to the GluR2 gene show reduced scanning and motor coordination. In these animals, the AMPA receptor-mediated synaptic transmission is reduced, but the long-term potentiation is better [34]. Knock-out mice to the GluR2 gene also exhibit increased cell death, possibly due to the excitotoxicity related to the greater insertion of the compensating homomeric GluR1 protein in AMPA receptors [35, 36].

### 4. Clinical features of epilepsy-associated autoimmune encephalitis

Each of the currently known neuronal cell surface or synaptic autoantibody associates with a specific syndrome or limited set off symptoms (Table 1). NMDAR antibody-associated encephalitis is a recently described disorder in which infrequent seizures are associated with the presence of autoantibodies directed against the extracellular domain of the NR1 subunit of the NMDAR. This disorder was first described as a clinical entity in 2005, in one in four young women who developed acute psychiatric symptoms, seizures, memory deficit, in association with the presence of an ovarian teratoma. In a study of 100 patients, it was shown that although the majority are young women (mean age 23 years), the disorder could occur in men and in children. This fact has allowed the number of pediatric cases to grow steadily and appears to represent approximately 40% of all cases [27, 37, 38].

#### 4.1. NMDA receptor

Symptoms of anti-NMDA receptor encephalitis develop and resolve in a multi-stage process; most patients experience a prodromal similar to a viral picture, which is followed by a pattern
<table>
<thead>
<tr>
<th>Epilepsy-associated antibody</th>
<th>Anti-LGI1 vs. LGI1 (Channels Ke+)</th>
<th>Anti-CASPR2 vs. CASPR2</th>
<th>LGI1 &gt; CASPR2 (VGKC-complex) vs. LGI1 &gt; CASPR2</th>
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<th>AMPA vs. GluR1/2</th>
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<tbody>
<tr>
<td>Gender/Age of involvement</td>
<td>M &gt; F</td>
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<td>F &gt; M</td>
<td>F &gt; M</td>
<td>M &gt; F</td>
<td>F &gt; M</td>
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<tr>
<td>&gt;50 years</td>
<td>&gt;70% childhood</td>
<td>&gt;20 years</td>
<td>&gt;40 years</td>
<td>&gt;40 years</td>
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</tr>
<tr>
<td>Clinical manifestations</td>
<td>Hyponatremia. Cognitive impairment. It is associated with the presence of a thymoma or SCLC</td>
<td>Morvan syndrome Complication with Myasthenia gravis Not associated with neoplasias</td>
<td>TLE Hyponatremia and Synchronus dystonic arm posturing and grimacing facial ipsilateral associated with paraneoplasias (thymomas and lung cancer (SCLC)).</td>
<td>Viral pathway: fever, headache and fatigue of infectious etiology, delirium and disorientation. 10-20 days of evolution: oro facial dyskinesias, choreoathetotic movements, nystagmus, decreased consciousness and dysautonomia</td>
<td>Diabetes mellitus type I, Stiff- person syndrome, cerebellar ataxia, non-paraneoplastic LE Severe cognitive impairment</td>
<td>It is associated with the presence of SCLC, thymus and breast cancer tumors</td>
<td></td>
</tr>
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<td>Psychiatric comorbidity</td>
<td>Confusion and behavior and REM sleep disorders</td>
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<td>Sub-acute amnesia, confusion, sleep disorders, psychosis, anxiety, personality changes and depression</td>
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<tr>
<td>Seizure activity</td>
<td>GTC</td>
<td>GTC</td>
<td>GTC</td>
<td>GTC</td>
<td>CPS</td>
<td>CPS</td>
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<td>GTC</td>
<td>FBDS</td>
<td>GTC</td>
<td>CB</td>
<td>CPS</td>
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<tr>
<td>CPS</td>
<td>SE refractory to treatment</td>
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<tr>
<td>Electrographic activity (EEG)</td>
<td>Slow focal or generalized activity</td>
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<td>Focal or diffuse delta/theta activity and delta brush activity</td>
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**Diabetes mellitus**
- Type 1
- Stiff-person syndrome
- Cerebellar ataxia
- Non-paraneoplastic LE
- Severe cognitive impairment

**Psychiatric comorbidity**
- Confusion and behavior and REM sleep disorders
- Cognitive impairment, memory loss and hallucinations
- Sub-acute amnesia, confusion, sleep disorders, psychosis, anxiety, personality changes and depression
- Personality changes, hallucinations (visual and auditory), difficulty speaking
- Depression and anxiety.
- Cognitive impairment, behavioral disorders such as psychosis and hallucinations
- Confusion, amnesia, disorientation and psychosis

**Seizure activity**
- GTC
- FBDS
- GTC
- CPS
- SE refractory to treatment
- GTC CPS

**Electrographic activity (EEG)**
- Slow focal or generalized activity
- Slow focal or generalized activity
- Slow focal or generalized activity
- Focal or diffuse delta/theta activity and delta brush activity
- Slow focal or generalized activity
- Slow focal or generalized activity
- Focal activity

**Clinical manifestations**
- Hyponatremia
- Cognitive impairment
- Complication with Myasthenia gravis
- Not associated with neoplasias
- TLE
- Hyponatremia and Synchronus dystonic arm posturing and grimacing facial ipsilateral associated with paraneoplasias (thymomas and lung cancer (SCLC)).
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<th>AMPA vs. GluR1/2</th>
</tr>
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<tbody>
<tr>
<td>Treatment and prognosis</td>
<td>Good response to immunotherapy</td>
<td>Good response to immunotherapy</td>
<td>Good response to immunotherapy</td>
<td>Slow response to Immunotherapy with recurrence</td>
<td>Refractory to treatment with AED’s and immunotherapy</td>
<td>Good response to immunotherapy with recurrence</td>
<td>Good response to immunotherapy with recurrence</td>
</tr>
<tr>
<td>References</td>
<td>[49, 54–56]</td>
<td>[31]</td>
<td>[31, 55, 58, 65, 67]</td>
<td>[59–61]</td>
<td>[31, 51, 57, 62, 64]</td>
<td>[34, 57, 61, 66]</td>
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NMDAR, N-methyl-D-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin-associated protein-like 2; AMPAR, amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABA<sub>α</sub>/β R, gamma-aminobutyric acid A/B receptor; mGluR1/2, metabotropic glutamate receptor type 1/2; LE, limbic encephalitis; SPS, stiff-person syndrome; CPS, complex partial seizure; EEG, electroencephalogram; FBDS, faciobrachial dystonic seizures; GTC, generalized tonic-clonic.

Table 1. Neuronal cell surface autoantibodies, associated epilepsy, and the clinical symptoms.
of memory alterations, behavior, cognition, developing psychotic pictures, convulsions, dyskinesia (orofacial, trunk, and limb), and autonomic respiratory instability. Most adults are initially seen by psychiatric services and may be confused with acute psychotic disturbance or drug abuse. Most children are taken to medical care due to changes in mood, behavior and/or personality, seizures, or language impairment [38–40]. Autonomic instability is a common manifestation in adults. Some patients develop severe cardiac arrhythmias that require the use of pacemakers. Signs of more frequent autonomic dysfunction in children include urinary incontinence and sleep disturbances [38]. Nuclear magnetic resonance (MRI) findings in these patients may be hyperintensities in FLAIR or T2 sequences in the cerebral cortex, cerebellar or temporal medial lobes, as well as in the corpus callosum and brainstem. In some cases, a transient increase in contrast, of the cerebral cortex, cerebellum, basal ganglia and meninges is observed.

Movement disorders are common and can be misinterpreted as a convulsive activity, the most common being dyskinesia, usually orofacial, choreoatetoid limb movements, rigidity, opisthotonos, or a combination of these. In most patients, EEG shows a slow generalized activity, disorganized without ictal discharges. These findings may overlap with ictal discharges in the EEG [41]. Niehusmann and colleagues [42] reported presence of NMDAR-antibodies in women (age range, 15–45 years), which had extra-temporal epilepsy, a reduction in level of consciousness and altered speech, as well as nystagmus, dyskinesia, dystonia, and hypventilation. Clinical improvements in seizure frequency were seen in treatment of three patients treated with an immunomodulator such as corticosteroids and IVIg.

4.2. GABAb

GABA receptors are essential to inhibition. The presence of autoantibodies against these receptors has been associated with seizures and changes in memory and behavior. In a study with 15 patients with GABABR and LE antibodies (median age of 62 years, range 24–75 years), the clinical features where the presence of seizures, confusion and altering memory. Seizures were the predominant characteristic in 87%, and were mainly onset of temporal lobe with secondary generalization. 13% of patients presented epileptic status. CSF findings showed lymphocytic pleocytosis (n = 4) and MRI showed an increased signal, typical of LE. Clinical improvement was observed in 40% of patients who received IT alone and 20% who had IT, and 46% of patients were taken for a surgery to remove tumors. On the other hand, in a series of 15 patients, the mean age of presentation was 62 years (range 24–75) and both sexes were equally affected. About half of the patients had an associated tumor, either a small cell lung carcinoma or a neuroendocrine lung tumor. These patients often have additional antibodies to glutamic acid decarboxylase (anti-GAD) and several non-neuronal proteins of uncertain significance, suggesting a susceptibility to autoimmunity [32, 43].

4.3. AMPA receptor

Antibodies to the AMPAR have recently been described in patients with limbic encephalitis (LE). The AMPAR antibodies are the least frequent of these antibodies, however, also these patients develop a limbic dysfunction that may be associated with significant psychiatric
symptoms. The most common disorder effects were in the middle-aged women. Most patients present with a sub-acute appearance of confusion, disorientation and memory loss, and seizures may also be part of the clinical describe. About 70% of patients have an underlying tumor in the lung, breast, or thymus. AMPAR is the predominant receptor subtype in the hippocampus, and it has been found that these antibodies in patients caused a decrease in the pre- and postsynaptic GluR1/2 receptor groups in cultures of rat hippocampal neurons. Since the receptor levels have been more affected at synapses than along dendrites, the findings suggested a mechanism by which patients’ antibodies disrupted the receptor traffic, moving them from synaptic sites to extra-cellular sites and intracellular pool. These effects are similar to neuronal plasticity models that decrease synaptic strength, also called long-term depression. The effects of the antibodies were shown to be reversible [42, 45].

4.4. GAD

Glutamic acid decarboxylase (GAD) is a cytoplasmic enzyme that catalyzes the conversion of L-glutamic acid to gamma-aminobutyric acid (GABA), considered the main inhibitory neurotransmitter of the central nervous system. GAD is expressed primarily in GABAergic neurons and in pancreatic β cells, and has two isoforms with different molecular weight; GAD65 and GAD67. GAD antibodies act as a marker of the underlying autoimmune disease, although it is not known how antibodies against an intracellular enzyme can directly initiate pathological events; however, it is known that anti-GAD Abs inhibit the activity of GAD, and the synthesis of GABA antibodies to GAD is associated with several autoimmune disorders, including limbic encephalitis [44, 45], type 1 diabetes mellitus [46], Stiff Person Syndrome (SPS) [47], and cerebellar ataxia [48], as well as overlapping syndromes. Recent work highlighting the response of these patients to immunotherapy and association with forms of epilepsy related to localization suggest that antibodies may also be present with specific cell surface. This is supported by a functional study of magnetic resonance spectroscopy in patients with TLE and elevated levels of serum GAD antibodies that demonstrated significantly lower GABA levels within their cortex compared to paired control patients [44]. On the other hand, in one study with 138 patients over 18 years old, investigated with recent onset epilepsy, were prospectively studied to determine the clinical and radiological characteristics of LE, and response to treatment. Fifty-three adult patients fulfilled the criteria for LE; nine had high-titer GAD antibodies and ten had voltage-controlled potassium channel (VGKC) antibodies. Patients with GAD antibodies were younger’s (range, 17–66 years) and had seizures only, whereas polymorphic limbic features were more frequent in the VGKC positive group. Patients with anti-GAD antibodies had more frequently oligoclonal bands of cerebrospinal fluid and intrathecal secretion of the specific antibody. Which after monthly, patients were treated with intravenous methylprednisolone pulses, however GAD antibodies remained elevated in 6/6 patients, however VGKC antibodies normalized in 6/9 patients (p < 0.03). Despite the more intense anticonvulsant treatment in the group with anti-GAD antibodies (p < 0.01), none of these patients were seizure free, unlike all patients with VGKC antibodies (p < 0.001). High-titer GAD antibodies define a form of non-neoplastic LE. It is a chronic non-persistent disorder, and should be included in the differential diagnosis of patients with LE and mediotemporal encephalitis [49].
4.5. LGI

Studies describing treatment of LGI1-antibody associated encephalopathy, LGI1 is a protein secreted by neurons that interact with pre- and postsynaptic receptors. LGI1 mutations have been associated with autosomal dominant temporal lobe epilepsy syndrome [50, 51]. Patients with antibodies against LGI1 develop alterations of memory, confusion, and seizures. The MRI results are typical of limbic encephalitis. Memory and cognitive deficits can be preceded by brief tonic seizures that can be confused for mimetic myoclonic movements. Observational studies have provided evidence of a marked improvement with high-dose steroids, IVIG and PLEX for patients with auto-antibodies to LGI1 and CASPR [37, 50–52]. In a retrospective study of 10 patients with high titers of VGKC-complex antibodies that had seizures and memory disorders, who received IVIG 2 g/kg/day, 100 mg prednisolone on alternate days and PLEX for 5 days, improvement was observed in frequency of seizures and cognition in six patients within 2 weeks to 12 months, correlating with reductions in antibody titers [37]. Earlier treatment, and possibly corticosteroids, appeared to provide greater benefits than before. This disorder had been included previously within the spectrum of antibodies against voltage-dependent potassium channels. Some patients develop hyponatremia and behavior or REM sleep disorders. Only 20% of cases are associated with a neoplasm, usually thymoma or small cell lung carcinoma.

5. Diagnostic approach

The laboratory diagnosis of AD depends on the identification of the clinical symptoms of the patient, their association with each disease and their correspondence with the detection of AA. For this reason, laboratory tests are of great importance for the evaluation of patients when an AE is suspected. The results can confirm the diagnosis, estimate the severity of the disease, and are useful to follow up its evolution and establish a prognosis. The presence of autoantibodies (AA) alone in a patient does not mean the diagnosis of an AD, the associated signs and symptoms help to achieve the definitive diagnosis and are of crucial importance. Analysis of CSF plays a central part in all diagnostic criteria for encephalitis, including infectious encephalitis, relevant antibodies might be found only in the CSF, because the repertoire of antibodies in the CSF and serum can be different in the same patient (e.g., NMDA receptor in CSF and serum) [52]. By other way, serological tests to detect AA have demonstrated the presence of AA in healthy individuals and in known non-EA patients and approximately half of all autoimmune encephalitis series are Ab-negative cases, so AA is a confirmatory diagnostic test, for this reason the diagnostic tests must be combined. Three basic research techniques are used for this purpose must include: tissue-based assay (TBA), cell-based assay (CBA), and immune-precipitation (IP; in-house). In the TBA, rat or mouse brains are stained with CSF or serum of patients with an indirect immunohistochemistry or immunofluorescence technique or the combination of two fluorophores, one that identifies the autoantibody and the other to the antigen and use of confocal microscopy (Figure 1(C)–(F)).
In the cell brain adhesion test (CBA), cells (e.g., HEK293 cells) are transfected with the respective neural antigens (receptors, channels, etc.) and incubated with the CSF or serum of patients with an indirect immunofluorescence technique. Autoantibodies to the specifically expressed receptor result in the cell membrane marking cells, similar, primary cultures of hippocampal neurons can be used, with these methods autoantibodies are displayed on the surface of the neuronal membrane [53].

For the detection of classical intracellular and cytoplasmic antibodies, the immunoblot technique is used. Immunoblotting is the method that uses Abs to detect a specific protein from a mixture of several unrelated proteins separated by molecular weight. The diagnosis of antibodies with this technique involves several steps, including protein extraction of mice brain tissue followed by (30–50 μg) spitted proteins through electrophoresis, and transfer of a nitrocellulose membrane and overlapping of the primary antibody (the serum or CSF of the patient) and secondary on the membrane labeled with enzymes (Figure 1(G)) or fluorescent antibodies [54]. Recently, we introduced flow cytometry and have confirmed that in those patients with AE, a large presence of activated T and B cells is observed; in some cases, the CD8+ cells are dominated and in negative cases, there is no activation of lymphocytes (unpublished data); the results suggest that this tool could provide additional information on the patient’s immune response (Figure 1(B)). On the basis of this data, the recommendation is to include both CSF and serum for citometric testing in patients with suspected autoimmune encephalitis.

6. Concluding remarks

Recently, several reports that associate CNS disorders with autoantibodies are directed against cell surface proteins, which are likely to be pathogens. Many of these conditions have seizures as an early and prominent feature, which are commonly refractory to conventional drugs. In contrast, a good response with immunotherapy is often observed. The studies in patients coincide in clinical manifestations, but not in autoantibodies. For this reason, CSF is crucial in the identification of new antigens, including NMDAR, AMPAR, GABABR, GABAARr, mGluR5, DPPX and LGI1, and Caspr2. Serum negativity is more likely with a milder form of the disease, presenting with clinical pictures of psychosis but not requiring intensive care, particularly if the antibodies are generated predominantly in the brain, which makes it necessary to standardize the diagnostic methods in order to be safer and to offer a timely diagnosis. The effects of antibodies on children (the effects of antibodies on hippocampal synapses) are different from that of adults; this may explain some of the differences in clinical pictures between adults and children. For this reason, the selection of patients for the autoimmune evaluation requires a high level of suspicion in the initial consultation. Since there have been currently no universally agreement upon diagnostic criteria for autoimmune epilepsies, the clinical evidence, such as the high frequency of seizures, psychiatric co-morbidity and resistance to AEDs, are important indicators to decide it. More studies are needed to identify early autoantibodies and to perform preventive treatments.
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