Autoimmunity, Seizures and Epilepsy: a brief systematic review

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Introduction: *Epilepsy is un chronic neurologic disorder marked by recurrent convulsive seizures. It is one of the most prevalent neurologic disorders around the world. One of the etiologies that has become more relevant in the last few years is autoimmunity, which has explained many cases of idiopathic epilepsy or refractory to conventional treatments.* ***Methods:*** *an advanced search associated to filters at the platform PubMed with the terms "epilepsy" and "autoimmunity" was made. 17 articles from a total of 98 published, from 2010 on were selected, those that provided more data from this physiopathology.* ***Results:*** *Based on literature, the main autoimmunity mechanisms causing epilepsy are described. Among them are generation of autoantibodies, deregulation of the cytokines profile and loss of control of T auto reactive lymphocytes. Such phenomenon causes neuroinflammation and is caused by infections, paraneoplastic syndromes, maternal autoimmunity transferred to the baby, autoimmune encephalitis, among others.* ***Conclusions:*** *During the last few years great progress has been made in understanding autoimmune epilepsy; however, there is still much to understand. Despite the promising discovery of antibodies, still there are many cases epilepsy with seronegativity, or cases with presence of antibodies, but not autoimmune epilepsy. It is important to highlight that some effective/specific diagnosis mechanisms must be determined in order to implement suitable and resolutive therapeutic protocols.*

Key Words: *Epilepsy, autoimmunity, antibodies.*

INTRODUCTION

Epilepsy is one of the most common neurologic diseases around the world. It affects people of all ages, and it is the third most usual disease, after Parkinson and Alzheimer[(1)]. Around 70 million people around the world are estimated to have this disease. It has an incidence of 67.8 cases every 100,000 inhabitants. Most of them are in more vulnerable countries, probably due to the higher risk caused by certain endemic conditions[(1,2)].

This disease may have its origin both, in congenital and acquired factors. Among the latter are cortical damage caused by traumatism, cerebrovascular accidents, neoplasies, genetic mutations, autoimmune diseases, infections of the central nervous system, among others. However, a significant percentage of people affected by epilepsy have an unknown etiology[(3)].

In time, autoimmunity as an etiology of epilepsy has become stronger, particularly for idiopathic forms or those refractory to

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conventional antiepileptic treatments, as a correlation has been established between systemic autoimmune processes and development of convulsions. A series of neuronal serumal autoantibodies or in the cerebrospinal fluid[4] have been discovered which are associated to typical epileptic phenotype, both in clinical practice and in RMI[5] findings. That is why the International League Against Epilepsy (ILAE) has recognized autoimmune epilepsy as a separated clinical, regarding its classification[6].

In this article we propose an updated view of the existing evidence on autoimmune mechanisms and biochemical findings involved in various epileptic syndromes, in order to put into perspective, the importance of this approach regarding comprehension of various clinical pictures, and also its relevant diagnosis/ therapeutical dimensions.

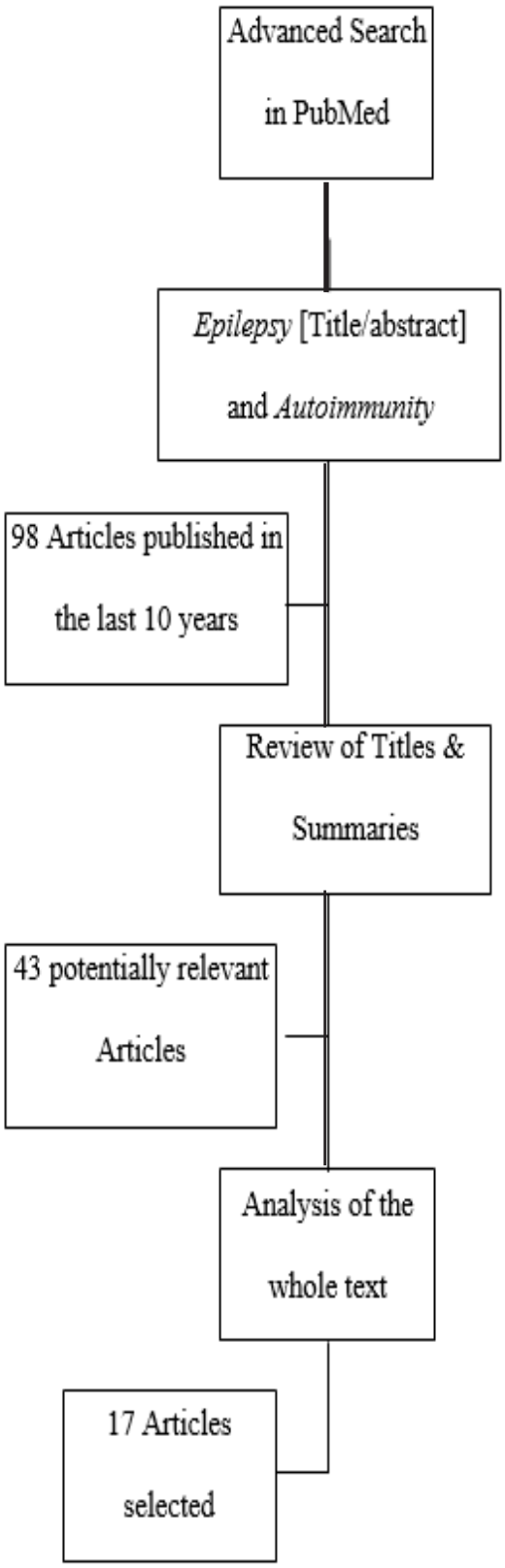
METHODS

An advanced search using the platform PubMed was made, using the terms "epilepsy" and "autoimmunity" in the title and in the abstract of the publication. Articles published during the last 10 years and performed in humans were included.

The initial search retrieved 98 articles. According to the analysis of the titles and summaries, 43 publications were preselected as they were part of the focus of this Article. After fully analyzing the texts, 17 articles were finally included as they were useful to describe the epidemiology and physiopathology of the autoimmune phenomenon involved in the evolution of this disease.

For making this text other 12 articles were quoted as conceptual support is required; 6 additional articles are quoted in the introduction in order to provide a wider vision about this topic.

Figure 1. Search & Selection Diagram



RESULTS

General Mechanisms

In the pathogenesis of various central nervous system disorders autoimmune mechanisms causing neuroinflammation are involved. This is the first step of various

pathological and clinical[7] events. The action spectrum the immune system may have in the development of autoimmune epilepsy is wide. It may go from the production of cytokines and pro-inflammatory chemokines causing a phenomenon of hiperexcitability associated to convulsions[7], or development of anti NMDA antibodies, among others to be specified in this document, which modify basal excitability of the neurons. Contrariwise, it has been described that convulsive seizures, in turn, generate malfunction of the hematoencephalic barrier, thus allowing cells to pass, such as T auto reactive lymphocytes[8].

In literature various antibodies related with appearance of epilepsy have been described, whether it is isolated or in the context of other autoimmune disorders[9].

These antibodies are linked both to surface antigens of the cell membrane, as intra cellular antigens, affecting the dynamics of synaptic complexes when binding to components, such as ion channels or to synaptic receptors of neurotransmitters[10].

Table 1 depicts various action mechanisms that have been correlated with various autoantibodies involved in development of autoimmune epilepsy.

AUTOIMMUNITY SOURCES IN EPILEPSY

Paraneoplasies

Some of the foregoing antibodies are produced in the context of paraneoplastic[5] syndromes. This has been explained as the tumoral tissue has molecularly similar antigens to those present in the nervous system. In this way the antitumoral response of the immune system is responsible for antigens compromise inside the encephalon. On the other hand, activation of T auto reactive lymphocytes by tumoral mediators would cause inflammatory and autoimmune phenomena as those previously described[11].

This is how the neoplastic context may cause cross cutting autoimmunity reactions, where antibodies against antigens produced by the tumor recognize nuclear and cytoplasmic antigens of the central nervous system, thus generating antibodies as a response by the immune system, just as described in Table 1, among them antibodies ANNA-1, anti CRMP-5, anti Ma2/Ta, anti amphiphysin are highlighted among others, which are mentioned in numerous studies describing its potential correlation with epilepsy[12].

In the central nervous system this molecular mimetism may cause various pathological expressions, such as limbic encephalitis and paraneoplastic encephalomyelitis (T auto reactive lymphocytes and onconeuronal antibodies), entities that may cause convulsions[11].

Infection caused by Herpes Virus

Infections caused by Herpesviridae, within the neurotropic pathogens, are a well-known cause of encephalitis as an epileptogenic factor. Apart from neuroinflammation, the capacity to induce autoimmunity against various components of the pre and post synaptic central nervous system due to crossed reactivity has been established, and by the formation of autoantibodies[13].

Particularly, antibodies against the receptor of N-Methyl-D-aspartate) at a serumal level and in the cerebrospinal fluid have been identified. However, cases of positive patients for infection of Herpes Virus simple 1 and 2 with seronegativity for autoantibodies against NMDAR in other type of viral infections have been reported[14].

Autoimmune systemic diseases

Although the first description of permanent/ provisional compromise of the central nervous system were made in patients with Hashimoto's thyroiditis, today there is evidence in various disease models, such as Diabetes Mellitus 1, Psoriasis, Rheumatoid arthritis, Graves Disease, among others[4,15]. Currently is estimated there is a risk 3.8 to 5.2 times higher to have epilepsy in the context of an autoimmune disease in adults and children, respectively[16]. In case of epileptic patients with systemic lupus erythematosus, the high values of anticardiolipin antibodies are correlated with a higher risk of convulsions. More generally, it has been observed that peripheral production of pro-inflammatory cytokines is related with appearance of convulsive events[4.17].

Figure 1. Search & Selection Diagram

Action spot	Antibodies
Intra cellular against nuclear and citoplasmatic antigen	ANNA-1 and ANNA-2. Anti Amfifisina. Anti CRMP-5. Anti Ma2/Ta. Anti GAD65.
Extracellular against neurotransmitter receptor, ion channels and synaptic proteins	Anti VGKC. Anti NMDA. Anti AMPA. Anti LGI1. Anti CASPR2. Anti Receptors of $GABA_A$ and $GABA_B$. Anti VGCC. Anti mGluR5 and mGluR1. Anti Ganglionic AchR Anti GFAP. Anti DPPX. Anti Receptor of glycine. Anti DNER. Anti DRD2. Anti MOG.

ANNA-1 and ANNA-2: Anti neuronal antibody, nuclear type 1 and type 2; CRMP-5: Collapsin Response-Mediator Protein 5; GAD65: glutamic acid decarboxylase; VGKC: voltage-dependent potassium channels.; NMDA: N-Methyl-D-aspartate ; AMPA: Acid α-amino-3-hidroxi-5-metilo-4-isoxazolpropionic; LGI1: Leucine-rich glioma-inactivated protein 1; CASPR2: Antibody anti Protein associated to contactin 2; VGCC: Antibody anti channels of calcium voltaje dependent; mGluR5 and mGluR1: Antibody anti Receptor metabotropic of glutamate 5 and 1; Ganglionic AchR: Antibody anti Receptor ganglionar of acetylcholine; GFAP: Antibody anti Protein of Glial fibrillary acid; DPPX: Antibody anti Protein similar to Dipeptidyl Peptidase; DNER: Antibody anti Protein similar to the Dipeptidyl Peptidase; DNER: Antibody anti receptor of Dopamin D2; MOG: Antibody anti glucoprotin oligondendrocytic of myelin

Maternal autoimmunity and epilepsy in Childhood

The correlation between rheumatoid arthritis in fathers or mothers and the occurrence of early epilepsy has been verified in series with about two million patients[18]. Additionally, it has been proposed that this early compromise could be caused by the transference of autoantibodies or active lymphocytes that, during the embryonic growth, would compromise structural integrity of the SNC[19].

Spread Acute Encephalomyelitis

It is a immune mediated disease characterized by a progressive demyelination and neurologic poli-focal symptoms, given mainly in children between 5-8 years old and generally it starts after 2 to 4 weeks of having a viral infection[21]. Its clinical scenario is varied and includes fever, cephalea and focal neurologic symptoms, such as convulsions, paresis, visual disturbances, among others[22]. There is a correlation between antibodies anti myelin oligodendrocyte glycoprotein (MOG) and spread acute encephalomyelitis[23]. Given this situation, the unleashed neuroinflammatory and demyelmating process may involve isolated convulsions[24] or even as an initial manifestation, in absence of full clinic and pathological episode[25].

Autoimmune Encephalitis

It is highly likely that with inflammatory compromise of the encephalon convulsions may appear. Next, various forms of encephalitis with autoimmune and/or inmunomediated etiologies are described:

- Encephalitis associated to antibodies anti NMDA: this is the most common encephalitis mediated by antibodies, which usually starts with an unspecified fever syndrome which changes within a couple of weeks into anxiety episode, hallucinations, loss of short-term memory and convulsions which are usually tonic clonic type. In time, this scenario turns into orofacial dyskinesia and affectation of the autonomous nervous system. The electroencephalogram shows generalized delta activity, while magnetic resonance evidence hyperintensities in neocortical areas, turning in time into generalized cerebral atrophy[15]. Encephalitis that, to a lesser extent, are associated to antibodies against Receptors GABAA[26], GABAB[27], mGlu5, AMPA, TPO (Thyroid Peroxidase), TG (thyroglobulin), GAD65, VGKC, etc[15] have been observed.

- Rasmussen's encephalitis: with chronic behavior chronic. It appears mostly in pediatric patients, affecting only one brain hemisphere. The inflammation usually causes refractory convulsions. Initially these are focal or unilateral, progressing till they become multifocal. These usually appear along with hemiparesis, aphasia, and cognitive deficit. At a molecular level, there are antibodies against the receptor of glutamate GluR3[4,28]. At anatomopathological level, it has been proved the presence of limited population of T lymphocytes in the brain, apart from inflammatory changes as perineuronal lymphocytes and clusters of perivascular T lymphocytes, and neurophagia[28].

- Epileptic syndrome related with fever infections (FIRES): Also known as New-Onset Refractory Status Epilepticus (NORSE) or Acute Encephalitis with repetitive partial seizures (AERRPS). It is featured due to fever episodes decreasing before a sudden start of convulsions. This podromal fever episode has been correlated with pneumonia and infections of the upper air way[29]. When analyzing the cerebrospinal fluid (LCE), pleocitosis, and high levels of proteins are usually found, but with no evidence of antibodies or positivity in fluids culture. However, high levels of cytokines, pro-inflammatory and proconvulsions chemokines have been described, such as IL-6, MIF (macrophage migration inhibitory factor), IL-8, CXCL10, among others[15,30].

Limbic encephalitis: regional inflammation of the encephalon, due to paraneoplastic infectious causes. This mainly affects the lobe temporal, although it may affect other lobe. Its main symptomatology is behavior and cognition alterations. In case of paraneoplastic etiologies onconeuronal antibodies have been described, such as Hu[31], Ma/Ta, CRMP5, Amphiphysin, VGCC, LGI1, among others[32]. Antibodies anti NMDA, anti GAD65[33] and VGKC have also been described which provide an autoimmunity character to this disease and whose manifestation usually includes convulsive crisis[15].

Diagnostic/Therapeutic Considerations under Development

Presence of autoantibodies is not conclusive in the diagnosis, as there are seronegative patients with symptomatology suggesting autoimmune epilepsy. Some of these cases may satisfactorily respond to immunosuppression[34]. In theory, detection of autoantibodies include detection of immunoglobulines against GAD65 (glutamic acid decarboxylase), and neuronal antigens, such as NMDAR and complexes of voltage activated potassium channels (VGKC), LGl complexes 1, and CASPR2 (contactin-associated proteinlike 2), among others, at serumal level and in LCR[4].

Imagery studies also provide information about encephalon inflammation. Magnetic resonance allows to identify inflammatory signs, such as edema, hypertension areas in T2 and FLAIR, catching of medium contrast, etc. Nuclear medicine techniques, additionally, (for instance PET with F18-flurodeoxyglucose (F-FDG-PET)), may identify areas of hypermetabolism when the cortex has an acute reactive state, or hypometabolism in atrophic areas. However, structural/functional results of magnetic resonance and F-FDG-PET may not be congruent[9,35].

At a therapeutic level, plasmapheresis has

proved to reduce convulsions frequency and improve neurological function, while treatment with corticosteroids, immunoglobulin, monoclonal antibodies, among others, have had incongruent results in Rasmussen´s Encephalitis[4.28]. Success, whether partial or total, of these therapeutical strategies is a wide proof of the role of the immune system, both in generation and in maintaining convulsive seizures and epileptic syndromes.

CONCLUSIONS

Epilepsy as a specific disease, and also relevance of convulsive seizures as a main/accessory clinical manifestation of various symptomatologies have prevalence enough to justify the state-of-the-art review in this field. Additionally, the estimated frequency with which autoimmune mechanisms participate in the generation of these cases, remaining as idiopathical to date makes possible to consider mechanisms described in this article, at least globally. Notwithstanding the foregoing, it is important to recognize that availability of serological measurements or imagery, necessary for the study with this approach, to date is usually limited in various clinical contexts.

Significant advances in understanding autoimmune mechanisms of the disease have been observed during the last few years, implementing possible therapeutical options in fields that, during the last decades were considered out of the medical treatment spectrum, observing new opportunities to influence the disease evolution and quality of life of the people affected. The various types of convulsive seizures and epileptic syndromes described here have a wide variability, regarding results of the serological, clinical and imagery study. That is why, in various areas of those encompassed in this article, the conclusive evidence is scarce. An updated view of the state of the art will give the reader a perspective of the investigation opportunities in this field and the relative significance of considering inmunomediated mechanisms for understanding clinical and therapeutical definitions.

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