

Immunotherapy for Treatment of Epilepsy

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ABSTRACT

Clinical and experimental evidence provided evidences for involvement of inflammatory processes in the brain in the etiopathogenesis of seizures. The innovative view is that brain inflammation may be a common substrate contributing to seizures in drug-resistant epilepsies of different etiologies, and recurrent seizures can per se be a major cause of long-term inflammation. The pathogenic role of immunity in epilepsies has been documented, based on observations of the efficacy of immune-modulating treatments. More recently, by the finding of inflammation markers including Autoantibodies (**Ab**) in persons with a number of epileptic disorders. On the other hand, the pharmacology has shown progress in terms of new drugs with broad spectrum of action

through different mechanisms anti-convulsants, and recently anti-epileptogenesis. Also, they have developed new minimally invasive surgical technologies, with lower risks of sequels, which facilitate seizure control. However, for certain forms of epilepsy, even these new technologies are insufficient to adequately control seizures and prevent deterioration associated with them. For this reason, they have used other approaches for adequate control of epileptic syndromes which are difficult to manage, among which it has immunotherapy, represented mainly by the use of immunoglobulin, steroids, and adrenocorticotrophic hormone. This chapter focused first on the description of the inflammation on epilepsy; secondly, we offer an overview of the evidence in experimental models of seizures to discuss how inflammation modulates epilepsy, and whether inflammation is always detrimental to cell survival. Thirdly, the therapeutic approach that has been used to try to control seizures mainly where there is a suspected circulation and epilepsy drug-autoantibodies.

Keywords: Epilepsy; Neuroinflammation; Immunotherapy; Autoimmune; Blood-Brain Barrier

INTRODUCTION

Epilepsy is a heterogeneous and serious brain disorder with multifactorial origins and manifestations. A brain disorder characterized by the presence of seizures, a spontaneous product of synchronous discharges of a neuronal population, which may be partial or secondarily generalized, whose main characteristic is the propagation area and the structures involved that give expression symptomatic [1,2], according to the World Health Organization, about 50 million people worldwide suffer from some form of epilepsy and finding is more prevalent in developing countries. In recent years, the relevance of immunological and inflammatory processes in the pathophysiology has been emphasized based on the results of immunotherapy and more recently, by the finding of inflammation markers including autoantibodies in individuals with a number of epileptic disorders [3-6].

Inflammation in Epilepsy

Inflammation is the immune system response to stimulation of various pathogens of endogenous or exogenous origin in the nervous system; the inflammatory response may be linked to damage, caused by the seizure activity or as a trigger for various disorders of systemic origin factor. It is characterized by the production of inflammatory mediators, resident tissue or immune competent cells circulating in the blood, which involves activation of innate and adaptive immunity.

In the brain, innate immunity is conferred by microglia, which acts as resident macrophages of the nervous system and represents the first line of defense against any damage. New evidence has shown that neurons and astrocytes also play an important role in inflammation [7,8] (Table 1). It is recognized that the CNS shows a strong inflammatory response not only to infectious

agents, but also to a wide range of injuries, such as those occurring after ischemic, traumatic or excitotoxic brain damage, or during seizures [8,10]. However, inflammation in the brain may have a neuroprotective function to promote homeostasis and repair damaged tissues; on the other hand, it can be detrimental to inflammatory mediators and promoting action [11]. The first failure neuroinflammation is associated with is over expression of molecules of Major Histocompatibility Complex (**MHC**) and microglia cells which express MHC class II (HLA-DR). Other adverse immune responses include the formation of autoantibodies against neuronal structures and changes in the characteristics of cellular and humoral immune response and in some pro-apoptotic proteins. The MHC plays a role in antigen presentation of T cells, which initiate and propagate the immune response, These cells can synthesize different cytokines, chemokines, trophic factors, components of the extracellular matrix and transmitters that can have either a protective or a detrimental effect on the adjacent neuronal cells, depending on the extent of injury or duration of exposure to pathogen [12]. Cytokines and chemokines initiate a cascade of proinflammatory signaling which ultimately leads to local vasodilation, extravasation and leukocyte recruitment, and activation of the adaptive immune response, in which microglia also play a role as presenting cells antigen [13].

Table 1: Experimental evidence of immunotherapy.

MEDIATOR	MODEL	EFFECTS	REFERENCE
IL-1			
IL-1 β (Agonis)	Kainic acid (Rat) Kindling (Rat)	Pro-convulsive	Maroso et al., 2010; 2011. Vezzani et al., 2013.
IL-1Ra (Antagonist)	Kainic acid (Rat) Pentylentetrazolium (PTZ). (Mice)	Anti-convulsive	Ravizza et al., 2008
Pralnacasan Vx-765 (ICE/caspase-1inhibitor)	Kainic acid (Rat) Kindling (Mice)	Anti-convulsive	Ravizza et al., 2006.
TLR4			
LPS(PAMP) (Agonist)	Kainic acid (Rat/Mice) Pentylentetrazolium(PTZ). Kindling (Rat) Febrile seizure (7-14 postnatal days)	Pro-convulsive (Acute effect) Decrease seizure threshold. (Long-term effect)	Ravizza et al., 2006; 2008. Akin et al., 2011
HMGB1(DAMP) (Agonista)	Kainic acid (Mice)	Pro-convulsive	Maroso et al., 2010
Box A (antagonis-tHMGB1)	Kainic acid (Mice)	Anti-convulsive	Maroso et al., 2011
LPS-RS LPS-Cyp (Antagonist)	Kainic acid (Mice) Pentylentetrazolium (PTZ).	Anti-convulsive	Ravizza et al., 2006;2008; Riazi et al., 2010

Signaling Pathways in Neuroinflammation

The inflammatory process in epilepsy has been described in experimental models and biopsies of patients with epilepsy, which has reported rapid induction of proinflammatory cytokines. By microglia, astrocytes, and neurons and by cells of the Blood Brain Barrier (**BBB**) and choroid plexus, after an acute event of seizures or Status Epilepticus (**SE**) mainly cytokines: interleukin (IL) -1β , IL-6, TNF- α (tumor necrosis factor alpha) [14]. IL-1 cytokine family is an important regulator of immunological and inflammatory reactions. The two molecular forms are IL-1 α and IL-1 β . The biological response to IL-1 is mediated by two specific cell surface receptors, namely RI and RII. The over-expression of IL-1 β activates the receptor IL-1 (R1), this activation is a trigger for changes in the short and long term in the convulsive threshold mainly in the hippocampus. This signaling pathway is involved centrally in the onset of tissue inflammation as an activator of innate immunity, is the first immune response to tissue damage or a pathogen and maintains basal levels under physiological conditions agent [14-16]. The immediate effect of the route IL 1-R / TLRs activated by IL-1 β after acute convulsive damage has also been reported in tissue from human hippocampus and experimental models that have shown decreased synaptic inhibition mediated by GABA in the region of CA3 and increase neuronal excitability mediated by NMDA voltage channels and permeable to Ca² ions in CA1, phosphorylation-dependent potassium channels (k⁺) followed by activation of p38 MAPK increasing function NMDA receptor using no transcriptional mechanisms and subsequent activation of Src kinase-dependent phosphorylation of NR2B, which hinders indirectly mediated inhibition mechanisms recapture and glutamate release in astrocytes [17,18].

The long-term effects of activation of the signaling pathway IL-1R / TLR triggering transcriptional changes that allow the perpetuation of the inflammatory response, which are mediated by NFK- β [19,20] which in turn generate a decrease gradual seizure threshold as well as cell death and subsequent induction of genes involved in the processes of neurogenesis, synaptic plasticity and neuronal reorganization. NFK- β turn promotes activation of cyclooxygenase-2 (COX-2) which is an important mediator of the inflammatory response; in experimental models reported their involvement in glutamatergic synaptic transmission, because COX-2 is an early gene that is constitutively expressed in pyramidal neurons of the hippocampus and cortex, and in the amygdala [21,22]. Excitatory stimuli such as seizures up-regulate (markedly or transiently) Cox-2 expression in neurons [5,23-25]. Recently, Sharma et al. reported an increase in the mRNA levels of two genes that have critical roles in Prostaglandin (**PG**) synthesis, Ptg2 (Cox-2) and Alox5ap, at 4 hours pos kainic induced seizures and at all post-KA treatment [6,26,27] (Figure 1).

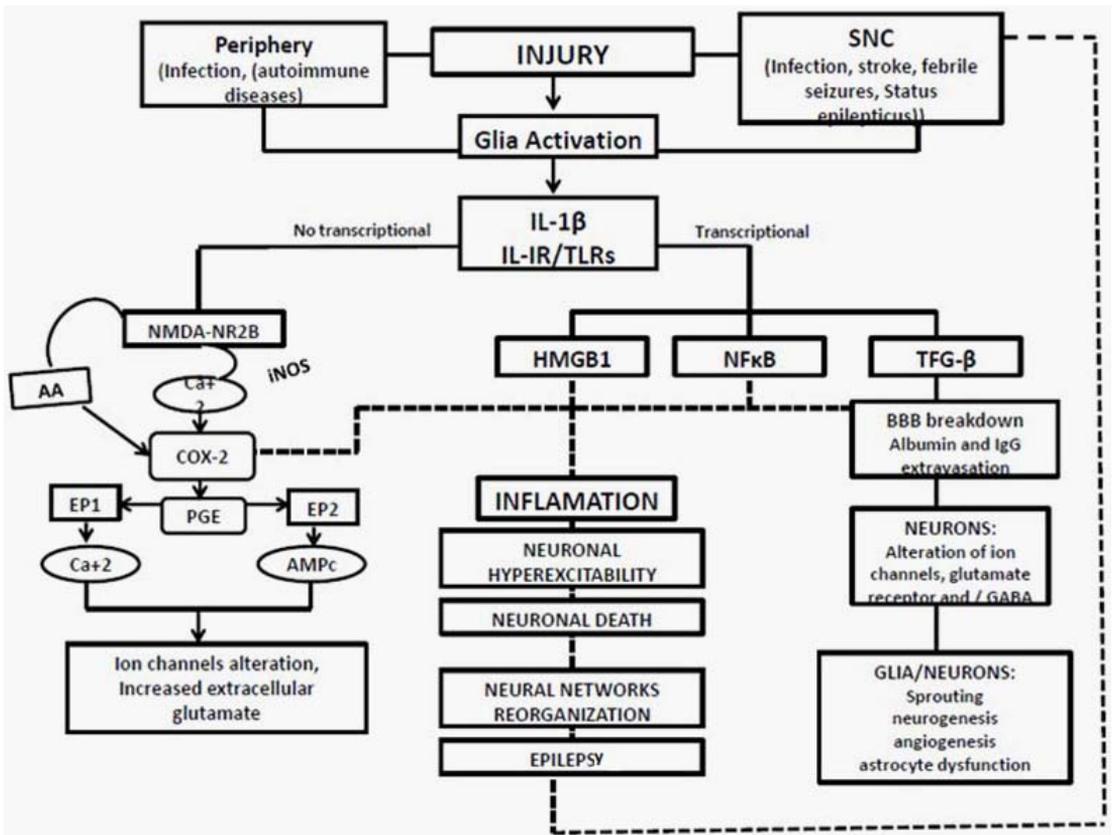


Figure 1: Representative image of neuroinflammation-by activation of the IL-1-R / TLR pathway activated by IL-1 β post-acute convulsive injury [6,8,36,67].

COX-2 can be activated in the first instance by IL-1R1 / TLR4, its expression increases one hour after a seizure through activation of NMDA receptors which promote activation of COX-2 by the route of inducible Nitric Oxide (iNOS) and phosphorylation of phospholipase A2 by producing Arachidonic Acid (AA) [27-31], its long-term activity is mediated by the presence of NFK- β which initiates transcription of genes encoding COX-2 and the synthesis of prostaglandins that facilitate the production of free radicals, as intermediate products that increase glutamate excitatory effect moreover, been reported that PGE2 production can also be activated by the expression TNF- α in the astrocytes, which in turn promotes the release of glutamate and contributes to neuronal hyper excitability [32-36].

Genetic Predisposition of Inflammation in Epilepsy

Numerous studies have attempted to establish associations between inflammatory response in epilepsy and presence of polymorphisms, studies in which if observed, genetic risk factors are Febrile Seizures (FS). Febrile seizures are those crises that occur in childhood from 3 months to 5 years of age resulting from a viral infection that does not directly affect the central nervous system,

without a previous unprovoked seizure meeting or other criteria for which acute symptomatic seizures are met. However, the presence of fever, suddenly fails. The two types of febrile seizures that occur in childhood are simple (primary generalized seizures lasting less than 15 minutes and not recurring within 24 h) and complex (focal onset, longer duration, and / or produced in a burst) [38].

A family member of the interleukin (IL) -1 are integrated by two pro-inflammatory cytokines (IL-1 α , IL-1 β) and the inhibitor of both (IL-1 receptor antagonist or IL-1 RA). Members of this family are located on the chromosome 2. IL-1 has a role in the development of inflammatory diseases and the induction of fever, which is evidenced by the use of inhibitors. The main association has been observed in the polymorphic changes of a cytosine for thymine (C> T) nucleotide single base rs16944, rs1143634, rs1143627 and in different neurodegenerative diseases like Alzheimer's or Parkinson [39,40]. The increase in transcript expression is associated with the IL-1 β -511T and IL-1 β -31C, although in both cases the associated nucleotide is the ancestral form or reference gene [41].

Two meta-analysis studies, one of them was done by Kauffman MA *et al* [42] included studies with Japanese, Finnish, German, Taiwanese and Turkish population, and after statistical analysis were able to identify the best genetic model between the different combinations of homozygotes (T / T vs C / C) or heterozygous (C / T. C / C or T / T vs. C / T), no association between any of the genotypes and epilepsy was observed in the other studies [43] besides the above populations that included the Chinese population, in which it was found that genotype TT vs. CC + CT IL-1 β -115 polymorphism, showed significant differences [odds ratio (95% CI) 3.97 (1.02 - 15.37)]. This association between genotype present in the Asian population and febrile seizures was recently confirmed by a study where no association between Caucasians and development of febrile seizures was found [43].

Interleukin-6 (IL-6), Tumor Necrosis Factor (**TNF**) and IL 10, are also involved in the regulation of fever. A study that included 92 Turkish infants (6 months to 6 years old) with simple and complex febrile seizures with and without family history of febrile seizures, which were compared with 98 controls, showed that -174 G allele frequencies and genotypes -174 GG and 572 GG position of the promoter region of IL-6 position of the promoter region of IL-6 were higher in patients; the -174 GG genotype frequency was higher in those with a family history of febrile seizures; and -597 GG genotype was higher in patients with complex febrile seizures compared to controls [44].

In more recent studies [45], 19 genes related to the inflammatory response were analyzed by mass sequencing (CASP1, IL-18, IL-1A, IL-1B, IL-1R1, IL-1R2, IL-1RN, IL-33, IL-6 , IL-6R, NLRP3, P2X7R, PTGER3, PTGES, PTGS2, TLR4, TNF, TNFRSF1A and TNFRSF1B). These included 98 cases of Caucasian infants with febrile seizures with simple febrile seizures and complex with familial or sporadic history. The results showed a nominal association between six SNPs (rs208294,

rs1718134, rs5030717, rs10752641, rs1409162 and rs5702) present in the P2X7R, TLR4, IL-6R, PTGER3 genes. The most significant association was presented at the SNP rs208294 of P2X7R gene where the change in C> T is presented in exon 5 and affects the protein (H155Y). However, it has a very low risk factor very low [odds ratio (95% CI), 0.63 (0.45 to 0.89)]. With respect to the other SNPs, none of them show a major risk factor that was identified [45]. The last findings show that there is a relationship between the presence of febrile seizures in childhood and temporal lobe Epilepsy with Mesial Sclerosis (**ELT + MS**) without being able to define so far if febrile seizures are the cause or consequence [46]. It is therefore interesting to identify molecules involved in inflammatory processes in this study (pathology), such as IL-1 β .

Autoimmune Epilepsy

An aspects that generate scientific interest today in the so-called “autoimmune epilepsies”, autoimmune disorders have long been recognized as potential causes of seizures. First, is finding a convincing pathophysiological explanation of what are the immune mechanisms that can produce epilepsy, its appearance still unresolved. Clearly, the involvement in the CNS produce acutely by an inflammatory process can produce an insult to the brain similar to encephalitis and trigger focal epilepsy. However, the problem is to determine which individual in the initial process will continue in a cascade of deregulating the immune system in the brain. Especially its main representative, the microglia; which can lead to a chronic inflammatory process of neuronal death, and uncontrolled epilepsy. For many years, Encephalitis Rasmussen was the model of epilepsy mediated immunity (GluR3), a progressive inflammatory epileptic encephalopathy which is rare and severe [47,48].

The report of an autoimmune basis led to the introduction of Immunotherapy (**IT**) in some Drug-Resistant Epileptic Syndromes (**DRES**) [49] prompted an intensive search for self-antibodies (**Abs**) in epilepsy. The findings of limbic Encephalitis (**EL**) associated with self-Abs against neuronal plasma membrane (receptors, ion channels) or intracellular proteins have further fueled this search. As seizures are a key the infestation manifest, these disorders serve as a model for understanding epilepsy-immune system interaction [49], evoking the possibility that such antibodies could only cause seizures in patients with epilepsy, and leading to the search for self-Abs in patients with DRES [50].

There are multiple entities in which autoimmune processes are associated with epilepsy. This relationship is observed in different contexts: 1) Systemic Autoimmune Diseases affecting the Central Nervous System (**CNS**) and producing epilepsy in a limited number of patients (lupus, sarcoidosis, Crohn’s disease and some types of vasculitis). 2) Diseases with an immunological basis predominantly in the CNS, in which epilepsy is associated with low frequency compared to other neurological manifestations (Vasculitis, multiple sclerosis and acute disseminated encephalitis), 3) Mediated CNS immune diseases in which epilepsy is the predominant manifestation (limbic encephalitis, paraneoplastic and non paraneoplastic disease, Rasmussen and other autoantibody mediated encephalitis). Some entities, such as the so-called “Hashimoto encephalopathy”,

would be an intermediate group. 4) Epilepsy in which an immune mechanism is described as an explanation of this disorder (West syndrome, Landau-Kleffner syndrome, mesial temporal sclerosis, non lesional temporal lobe epilepsy associated with antithyroid antibodies [47-53]. The immune mechanisms that can produce epilepsy are an aspect that is still unresolved. Clearly, the CNS is involved so acute inflammatory process can produce an insult to the brain similar to encephalitis and trigger a focal. Most data on pathogenetic mechanisms associated with the neuronal cell surface autoantibodies focus on the NMDAR- antibodies found in patients with anti-NMDAR encephalitis. These autoantibodies recognize an extracellular, conformation- dependent epitope region close to amino acid 369 of the GluN1 subunit of the NMDAR. The autoantibodies crosslink and internalize the NMDAR, which reduces the receptor density on the neuronal surface, resulting in neuronal dysfunction [54]. This process is reversible after removal of autoantibodies and may explain the good recovery of patients after immunotherapy [55]. This Auto-Abs has been also described with other biomarkers related with different types of epilepsy associated with autoimmune encephalitis, such as the anti-Hu, anti CV2, anti-Ma 2, anti-CRMP5, anti-Sox1 encephalitis, some type of cancer antibodies, described in paraneoplastic limbic encephalitis, which have allowed typifying a biological marker in two entities (testicular and pulmonary cancer). Similarly, it has been shown that anti potassium channels and anti decarboxylase -glutamate (anti-GAD) auto- antibodies are associated with some forms of non paraneoplastic limbic epilepsy, producing TLE. In any case, their exact role in the pathophysiology of epilepsy is unknown and they are also found in other neurological diseases not associated with epilepsy (stiff-man syndrome). The importance of these markers is that they enable precise diagnosis of entities in which clinical data are sometimes the only specific finding, and they allow a more appropriate choice of treatment. Thus, diagnosis and treatment is possible of some associated tumors, with the use of immunomodulatory treatment and even immunosuppressants. In this sense, the presentation of a psychiatric condition associated with seizures in the temporal lobe in a young patient must be put on the track of some of these processes in the differential diagnosis, and early treatment initiated, with the use of both antiepileptic drugs as immunomodulators or immunosuppressant [56,57].

IMMUNOTHERAPY

Anti-inflammatory and immunomodulatory treatments have proven useful in patients with epilepsy with a clear immunological component. However, the problem lies in determining in which individuals the initial process will follow a cascade of dysregulation of the immune system in the brain, especially its highest representative, microglia, which can lead to a chronic inflammatory process, neuronal death and uncontrolled epilepsy.

The presumed immune therapeutic mechanism (ACTH, corticosteroids, plasmapheresis human immunoglobulin G, rituximab, azathioprine, and cyclophosphamide) is the removal of various neuroimmunological mechanisms involved. However, new models suggest suppression of endogenous brain agent's proconvulsant (neuropeptides) [58].

a) Corticosteroids: Are well recognized to exert important anti-inflammatory and immunosuppressive effects and they have been recognized to be possibly of benefit in a variety of childhood epilepsies. However, efficacy has been demonstrated in an infantile spasms [48]. Their immunological mechanisms are inhibition diapedesis and therefore infiltration of lymphocytes to the injured areas, attenuating production of inflammatory humoral mediators (IL-2) and inhibition of leukocyte function (helper T lymphocytes mainly) as well as endothelial cells. In short, immunosuppression prolonged use may bring about adverse effects such as iatrogenic Cushing's syndrome, hyperglycemia, Dyslipidemia, myopathy, Methylprednisolone is used at a dose of 1 gram per 24 hrs for 3-5 days [58-60].

b) Plasmapheresis: the activity of auto-Abs can be modulated by treatment with IVIGs and by plasma treatment, which consists of the mechanical removal of Abs by plasmapheresis (Plasma Exchange, **PE**) or by semiselective Immunoabsorption (**IA**). The patient's plasma is separated from the cellular elements of blood by centrifugation during PE and substituted by replacement fluid. Complement and cytokines removal of humoral components of the immune system, can modify cellular components, primarily in cell lines expressing Fc receptors, such as monocytes, macrophages, NK cells, but equally it has been discovered to impact on T cells. Plasmapheresis is not a selective removal of 150 grams neither of plasma proteins nor to removed 1g of pathogenic antibodies. There are rare complications, such as hemodynamic instability, dilutional bleeding disorders, hypocalcemia allergic reactions as well as those associated with placement of catheter thrombosis, infections, and sepsis, recommended neumatórxaxel regime and used by our center are 5 sessions every 48 hours. [8,59-61] IgGIV inhibits activation of innate cells, suppression of the production of cytokines proinflammatory, while increasing the synthesis of anti-inflammatory mediators. Blocking antigen presentation to stimulate T cells, acts directly by inducing apoptosis and inhibiting cellular responses TH1 lymphocytes, TH17 pathogenic, while increasing the expansion of T lymphocytes REG, in the same way it suppresses the production of pathogenic antibodies produced by B cells, the dose used is 2g / kg total infused for 2-5 consecutive days [61,62].

c) Human immunoglobulin G: Intravenous Immunoglobulin (**IVIG**) derived many donations from healthy individuals, consisting mostly of IgG, high range specificity of each of the donors, and very small amounts of IgM, IgA, and strokes soluble molecules. Including HLA and cytosines used in intractable epilepsies such as West syndrome, Lennox-Gastaut Syndrome, and infantile spasms. The mechanisms of action is multiple, IgG IV can address each compartment of the immune system, including cellular components (cells innate and adaptive immunity, endothelial cells, and NK cells) and factors Solubles (cytosines, chemokines, complement and pathogenic antibodies) IgGIV inhibits activation of innate cells, suppression of the production of proinflammatory cytokines, and soluble factors as tumor necrosis factor and interleukins induced by this factor. In endothelial cells and macrophages, suggesting a mechanism antiepileptic given anti-inflammatory medication; blocking antigen presentation to stimulate T lymphocytes acts directly inducing apoptosis and

inhibiting cellular responses TH1 lymphocytes, TH17 pathogenic, while increasing the expansion of T lymphocytes REG. In the same way it suppresses the production of pathogenic antibodies produced by B cells, the dose used is 2g / kg Total, infused for 2-5 consecutive days. However, the actual mechanism of complement and pathogenic antibodies) action is still uncertain. Case series show high effectiveness in controlling seizures in adult patients with Rasmussen's encephalitis; however, it does not seem as a dramatic response in children. Other studies show effectiveness in different syndromes with a decreased of more than 50 percent of seizures in 4-87 percent of patients, being more effective in patients with generalized and idiopathic epilepsies. A good answer is found in different series of patients with West syndrome, as an alternative when there are contraindications or adverse effects from the use of ACTH. There is no clear evidence of change in the electroencephalographic pattern [63,64].

a) Second line:

Rituximab: Is a murine monoclonal antibody against CD20 + cells, B-lymphocyte precursor, prior to a medical administration with acetaminophen and an antihistamine or corticoid steroid, the dosage to be used are 375 mg / m²SC, initial pulse and weekly replay 4 weeks [58,65].

b) Cyclophosphamide: is administered in a dose of 750 mg / m²Sc IV monthly with previous hydration and means application as a prophylactic measure for hemorrhagic cystitis main complication [58,65].

It should be noted that prior to immunotherapy treatment, ensure that meets with clinical criteria and tests positive for autoantibodies. The weight of immunotherapy should be taken into consideration against the importance of losing a potentially cause EFR treatable. This challenge is greater because of the difficulty of analyzing objectively the evolution of patients, since there are no biomarkers, reliable epileptiform activity. General values and self-neuronal Abs only reflect disease activity as inconsistent. Response rates were higher in patients with antibodies against antigens plasma membrane (93%) than in patients with or without intracellular antibodies (33%) antigens, while the delay in treatment was a negative prognostic factor. Long-term oral IT, led to a sustained reduction in seizures number > 80% of respondents for 6 months. These results are consistent with the known response to IT shown by patients with self-Ags surface antigens neuronal, as the receptor NMDA [52]. Further prospective studies in relation to the EFR autoimmune is to raise awareness of the role of IT in the treatment of refractory epilepsies

CONCLUSION REMARKS

Anti-inflammatory drugs have anticonvulsant efficacy in some cases of drug-refractory epilepsies, suggesting the possibility that chronic inflammation in the brain may be implicated in the pathogenesis of seizures and associated with long-term events. Recent knowledge on immune response of this type of epilepsy, allow us to enhance early therapeutic interventions, in order to avoid neurological sequelae of these patients. Usually, the start of the treatment is recommended

with first-line drugs, if paraneoplastic, you must perform diagnostic protocol and removal of the tumor. This measure will suppress the immune continuous stimulus, having the same remission of neurological symptoms that accompany neuropsychiatric autoimmune epilepsy. In other words, understanding the role of inflammation in developing resistant epilepsy has helped to change treatment schemes, even so there are many molecules that remain unexplored as anticonvulsant drugs. So it is necessary to carry out work that focuses on potential clinical application of anti-inflammatory treatments in order to improve existing therapy of this neurological disease.

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