



The Role of Interleukins in Epileptic Encephalopathies and Immunomodulation with Adrenocorticotrophic Hormone

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Abstract

Epileptic encephalopathies make up a group of electroclinical syndromes that are characterized by to have an established presenting age, clinical neurological deterioration secondary to persistent epileptic activity and an irregular response to classical pharmacological treatments. Its etiology is variable, and its precipitating factors are controversial. Since the 90's, the role of inflammation in epilepsy has been described, through to the findings like the presence of inflammatory cells and molecules in cerebrospinal fluid and surgical specimen from affected patients. Among the molecules that actively participate in this process we can find interleukins, which may be pro-inflammatory or anti-inflammatory and that may alter the permeability of the blood-brain barrier, modify the liberation of neurotransmitters and induce permanent neuroexcitation. The persistence of the neuronal excitability promotes the recurrence of seizure and refractoriness to the conventional treatments. This is why we propose that the effectiveness of the immunomodulation therapies in patients with epileptic encephalopathies might be due to control the subjacent inflammatory state.

Keywords

Epileptic encephalopathy, Inflammation, Interleukins, Immunomodulation, ACTH, Biomarker

Introduction

Epileptic encephalopathy is a condition where “the electric activity by itself contributes to a severe cognitive and behavioral deterioration of the patient beyond the expected for the subjacent pathology and susceptible to worsening in the future” [1]. It may present at any age, more severely during early ages considering its interference with the process of brain maturing. For diagnosis, it is necessary to demonstrate the alteration in the development and the loss of acquired abilities associated to epileptiform activity, except in patients whose syndromic diagnosis already includes the word encephalopathy [1]. The first case was reported in 1841 by Dr. West, who described the case of his son, which was characterized by spasms and setbacks in his neurodevelopment [2].

At the moment, several forms of epileptic encephalopathies are recognized, and some of them are mentioned in Table 1.

In the last few years research has provided findings that support the hypothesis that relates a poor regulation of immunological responses (innate and acquired) with the physiopathology of various central nervous system

Table 1: Epileptic encephalopathies.

| |
|--------------------------------------------------------------|
| Early Infantile Epileptic Encephalopathy (Ohtahara syndrome) |
| Early myoclonic encephalopathy |
| West syndrome |
| Dravet syndrome |
| Electrical status epilepticus during slow wave sleep |
| Myoclonic astatic epilepsy (Doose syndrome) |
| Lennox Gastaut syndrome |

(CNS) disorders [3,4] such as neurodegenerative diseases (Alzheimer's disease), autoimmune diseases (antibody encephalitis), cerebrovascular events and epilepsy [3-6].

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CNS Inflammation

Immunological activation in the brain is a physiological process that, during normal conditions, favors the modifications of synapses, neuronal plasticity and recovery from lesions, but a prolonged, exacerbated and uncontrolled response may be the cause of multiple disorders by the aforementioned mechanisms [5-7]. In these cases, the use of the term "maladaptive inflammation" has been proposed [7].

The blood-brain barrier (BBB) in a state of integrity limits the entrance of peripheral defense cells that may damage the nervous system, except activated T cells, against various aggressions [7].

Extrinsic events such as traumas, infection, and cerebrovascular events or intrinsic events like degenerative diseases or frequent epileptic activity may trigger the inflammatory cascade in the central nervous system. The immune response has some particularities here: since it does not have the same defense cells circulating in the periphery, others such as vascular pericytes and perivascular macrophages assume that role [7].

Microglia and astrocytes, in addition to their support, communication and nutrition functions in the neuronal microenvironment play a fundamental role in that cascade since they have the ability of activating after injury [7] and release chemokines, and to modify the expression of neurotransmitters and ionic channels in the cell membrane [8-10].

These aggressions on the CNS activate the innate and acquired inflammatory response [9] the first cells to participate are endothelial and glial cells with the synthesis of inflammatory molecules that increase the permeability of the BBB, favor the expression of adhesion molecules and act as chemotactics, allowing lymphocytes and neutrophils to pass through a barrier that has already been injured, besides the activation of the acquired response increasing cell damage [8,11-14]. The activated complement system induces the formation of membrane attack complexes (MAC), which form pores in the cell membranes of the neurons, microglia, oligodendrocytes and astrocytes favoring cell destruction [6,15].

While these phenomena may be common to various neurological pathologies and induced with the same mechanisms in animal models for different entities, each one has its own characteristics that explain its presentation and open the way for considering different immunomodulation therapies.

Inflammation in Epilepsy

In epilepsy, various findings show the existing relation between inflammation and epileptic seizure. In the first place, the demonstration through surgical speci-

mens of patients with Rasmussen syndrome from inflammatory infiltrates in the BBB. Additionally, it has been proven that the damage to the barrier secondary to any injury, including recurrent epileptic seizures, allow cells to pass from the peripheral immune system to the brain tissue, with the resulting activation of the microglia and the astrocytes, which is a key phase in the generation of a seizures [9,12,16].

Furthermore, in highly epileptogenic tissues like cortical dysplasias, the perilesional tissue of the tubers in the tuberous sclerosis complex and hippocampal sclerosis in temporal lobe epilepsy, the presence of different inflammatory mediators that participate in the innate and adaptive immune response such as chemokines (mainly CCL2, CCL3, CCL4, CXCR4, CXCL12), adhesion molecules (VCAM-1), activation of the COX2 way, NFkB, complement, acute phase proteins like HMGB1, activation of TLR-4 and interleukins has been proven and will be delved into below [12,14,16-18]. Chemokines type CCL2 and CCL3 are produced by astrocytes, perivascular microglia and infiltrated leukocytes. These cells facilitate the passage of monocytes, polymorphonuclears, T cells and dendritic cells through the BBB [12].

Once the primary aggression takes place and the activation of CNS cells occurs, the excitotoxicity cascade happens, leading to an increase in the glutamatergic activity and a decrease of the GABAergic inhibition, an alteration in the function of the ionic channels responsible of attaining neuronal homeostasis, such as those of potassium, and a limitation for the glutamate reuptake by the astrocytes, which is the neuronal mechanism for the auto-regulation of the synaptic microenvironment [14].

Studies in murine models for epilepsy have confirmed the existence of active inflammation preceding the onset of the seizures and persistent with time, evidencing the double role as cause and consequence of epilepsy. In this inflammatory microenvironment, molecules like interleukins, interferon, TNF- α , COX2 derivatives and growth factors are found, and they initially cause an alteration of the neuronal function and, chronically, neuron, microglia, oligodendrocyte and astrocyte damage and death, which perpetuates inflammation and epileptic seizure [5,9,19].

Interleukins in Epilepsy

In the physiopathology of epileptic seizures, interleukins also participate, proteins produced mainly by leukocytes, which act as second messengers and intervene in the activation and functioning of the immune system. In the CNS, they have been seen to interact in a paracrine and/or endocrine manner with the glia, modifying glioneuronal communication, increasing glutamate availability, promoting the transcription of genes related to

the glutamate receptors and activating astrocytes, which favors a permanent neuronal excitability state [5,20,21]. Along with various inflammatory factors like TNF- α , IL-1 and IL-6, they stimulate the secretion of the corticotropin releasing hormone (CRH), which has been related to the increase of epileptic activity, mainly in West syndrome [22,23].

Aside from their role in favoring neuronal hypersynchrony, interleukins are related to the refractoriness to treatment by different mechanisms that favor excitability and reduce inhibition. In the first case, an increase in the release of excitatory neurotransmitters and a decrease in their uptake, an increase in the expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the synaptic membrane due to an increase in the transcription of the corresponding genes are produced. They also induce the activation of the G protein associated to ionic channels, which modifies potassium and calcium currents in the neurons and glia, increase some neurotoxic metabolites like quinolinic acid, which is a tryptophan degradation product and act as an antagonist for NMDA receptors [4,21,24,25]. Additionally, there is a reduction in GABAergic receptor currents in the hippocampus and GABA receptor endocytosis is favored, [26,27] promoting a state of hyperexcitability. In murine and porcine models, prolonged exposure (> 6 hours) to inflammatory IL, such as TNF- α , have been confirmed to favor the expression of glycoprotein 2 in endothelial cells of the BBB, an element in charge of preventing the passage of various drugs like antiepileptics. This explains the difficulty that may occur with time of achieving an adequate response to anticonvulsant drugs [28,29].

Another important action of IL is the inhibition of long-term potentiation, which affects learning, memory and neuronal plasticity processes. While neuroinflammation is required for synaptic remodeling in the learning process during normal conditions, when there are pathological events like epilepsy, it interferes with the creation of new synapses, the production of neurotrophic factors, and neuronal excitability required to consolidate memory. In this type of affectations, it has a fundamental role in the overproduction of IL-1 and IL-6 [30,31].

Among the interleukins that have been found to be highly related to the presence of epilepsy in animal models and human studies, as facilitators or modulators of the crisis, we have IL-1, IL-1RA, IL-6, IL-7, IL-10 and IL-17, which have been reported in surgical pieces of patients with temporal lobe epilepsy, in dysplasias and cortical tubers, febrile seizure and some cases of epileptic encephalopathies, mainly in West syndrome [32-34].

Below we mention relevant aspects of these molecules.

Interleukin 1 (IL-1)

Even though it is majorly produced in the periphery and spread to periventricular organs to exert its action in the CNS, it is also produced in neurons and glial cells. It acts in the interleukin 1 receptor type I (IL-1R1), which has a close relation with N-methyl-D-aspartate receptors (NMDA) in hippocampus pyramidal neurons, modulating glutamatergic transmission. It increases neuronal excitability and decreases the convulsive threshold by means of the phosphorylation of channel subunits, which favors the entrance of calcium [5,25,35]. In the astrocytes, IL-1 increases the release of glutamate and inhibits its reuptake, it restricts the inhibition mediated by gamma-aminobutyric acid (GABA) and stimulates the release of IL-6, which has a convulsive effect [5,24,35].

It also acts in the glia and the astrocytes, activating the expression of genes that favor gliosis and modify the permeability of the BBB. It has also been proven that it induces the expression of high-mobility group protein B1 (HMGB1), which plays an important role in the permanent activation of the inflammatory response in epilepsy [6,20,26].

It has been found to be increased in focal epilepsy, mainly in temporal lobe epilepsy, and to be related with the presence of febrile seizure [20].

Interleukin-1 receptor antagonist (IL-1RA)

Interleukin-1 receptor antagonist is a molecule that prevents all the effects caused by the activation and action of IL-1 [9,26,36]. It is considered that its production is related to seizures regulation mechanisms given the fact that it is produced hours after the appearance of IL-1 in a proportion even 100 times higher [20]. In the study by Yamanaka, *et al.* [36] an increase in the levels of IL-1RA in relation to clinical and encephalographic improvement of the seizures in children with West syndrome after the immunomodulating treatment was observed.

Interleukin 6 (IL-6)

In animal models, a relation between the increase of seizures susceptibility and the increase of the antagonist effects of glutamate has been found. Additionally, a relation between astrogliosis and a decrease in the number of inhibiting interneurons and the proliferation of astrocytes has been reported. At the same time, it stimulates the release of corticotropin hormone from the pituitary, which has an independent convulsive effect. During clinical practice, an increase in the values after tonic-clonic seizures in patients with epileptic encephalopathies has been reported [9,27,37,38].

Interleukin 7 (IL-7)

It intervenes in maintaining the inflammatory re-

sponse by favoring proliferation, survival and differentiation of proB cells and regulating the growth of T cells [37,39,40]. Due to this, an important role in epilepsy has been stated for it. In a study where samples from adult patients with temporal lobe epilepsy were evaluated, elevated values of this interleukin were reported [41].

Interleukin 10 (IL-10)

Its anti-inflammatory role is widely known due to its inhibition of the synthesis of the cytokines and proinflammatory agents like IFN- γ , IL-2, IL-3, IL12, TNF- α , granulocyte-macrophage colony-stimulating factor (GM-CSF) and reducing the expression of the major histocompatibility complex class II [22,42]. This has led to postulate this IL is a neuroprotector because it inhibits the inflammatory response produced during seizures [20].

Interleukin 17 (IL-17)

It is part of a big interleukin family (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F) and has a proinflammatory action. Type A deserves some interest due to its action on the CNS by activating the glia and stimulating the release of proinflammatory molecules. It also induces neuron death and damage to the BBB on its own [43-45].

All of the above shows that these are key elements in the physiopathogenic process of epilepsy and that they may be potential biomarkers given the fact that they are molecules that are constantly produced during the process of the disease and are modified with the response to treatment. On the other hand, they could be used for monitoring the epileptogenesis process, the severity of the disease, the risk of complications or deterioration and as a follow-up element in the evaluation of the response to treatment and prognosis [46-48]. There is special emphasis on IL-1, IL-1Ra, IL-10 and IL-17, which have been found altered more frequently and with reproducible results in cases of epileptic status. This opens the expectation for tests that predict the response to treatment and the severity in this condition [3,5,6,8,9,12-14,19].

Moreover, the most studied epileptic encephalopathy from this point of view is the West syndrome where there is strong evidence indicating that inflammation plays a fundamental role in the presence and perpetuation of crises. This may be evidenced by means of high proinflammatory interleukin values and decreased anti-inflammatory values, reporting elevated values mainly for IL-1 β [33], IL-12 [33,49], IL-6 [33,50] and a decrease in IL-1RA [51], This justifies the need to consider treatment with immunomodulators like ACTH early in this epileptic syndrome.

ACTH and Immunomodulation

Nowadays, inflammation is one the studied therapeu-

tic objectives for the control of epilepsy, especially in epileptic encephalopathies, where clinical deterioration in the patient is progressive and its management is difficult and frequently poorly effective [4,48,52-54].

Among the proposed immunomodulation strategies that have been widely studied and that have shown efficacy in seizures control at experimental and clinical level we may find immunoglobulin G, methylprednisolone, prednisolone and adrenocorticotrophic hormone (ACTH).

ACTH is a hormone that is released naturally by the pituitary through the stimulus of the corticotropin releasing hormone (CRH) during a stressful event. ACTH in its plasma state is in charge of stimulating the release of glucocorticoids by the adrenal gland, with the capacity of modifying the function of the receptors of the neurotransmitters and the neuropeptides in the CNS. As such, it fulfills a neuromodulating and immunomodulating action intervening in the inflammatory process [32,55,56].

The mechanisms why it fulfills these functions are stated as follows:

From the neuroendocrinological point of view:

- I. It induces the synthesis of peripheral glucocorticoids, which are capable of passing through the BBB and acting on its receptors in the CNS, modifying the voltage dependent calcium channels currents [57].
- II. It stimulates the synthesis of neurosteroids by the neurons and the glia, which act as positive allosteric modulators of GABA receptors [9,55,57].
- III. They inhibit the release of CRH in the hippocampus, which has a proconvulsing action mainly in the immature brain, favoring glutamatergic transmission, reducing the periods of synaptic hyperpolarization and inducing the expression of proinflammatory IL receptors [9,54,55,57].

And as a neuroimmunomodulator it has the ability to:

- I. Regulate the proliferation, apoptosis and cell differentiation by means of the induction of enzymatic acetylation [55,57,58].
- II. Control the expression and release of neurotransmitters and neuromodulators.
- III. Diminish the susceptibility to seizure through the maturing of the myelin and dendritic formations [9,55,58].
- IV. Diminish the production of IL and cellular lymphocyte activation [9].

In infantile spasms, the application of ACTH is considered one of the preferred treatments [59] and has

shown clinical improvement in approximately 50% of cases, with spasm remission, normalization of electroencephalic findings and neurodevelopment improvement. The relapse ratio is variable and depends on the etiological diagnosis, the dosing and duration of the treatment [51-55,57,60-66]. Furthermore, there are reports of effectiveness of the treatment in other type of epileptic encephalopathies like the Landau-Kleffner and the Lennox-Gastaut syndromes and other encephalopathies with different causes and characteristics [67-71].

The correlation between clinical improvement in patients receiving ACTH and changes in the inflammatory response has been made through the measurement of interleukins given their constant expression in some epileptic syndromes like the West syndrome. In patients with good clinical and electrical response to pharmacological treatment, a decrease in proinflammatory IL, such as IL-1, IL-6 and IL-12, and an increase in anti-inflammatory interleukins like IL-1RA have been found [33,36,49,50,71]. In some publications, the response to ACTH has been higher than with other corticoids, which can be explained due to its multiple mechanisms at immunological and endocrine levels.

Specifically, in the West syndrome, the use of ACTH has shown not only a real control of the seizures at short and medium-term, but also improvement in the neurodevelopment process in these children. The proposed mechanisms range from improvement of neuron function when controlling hyperexcitability to considering that the regulation of high proinflammatory activity that hinders development and synaptic connectivity returns to base conditions, which provides an optimal environment for various learning processes [31].

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Inflammation has a fundamental role in the processes that affect the CNS, particularly in epilepsy, promoting the generation and persistence of crises after an initial trigger. This inflammatory response that is initially produced to delimit the damage and recover function in the affected tissue can be established indefinitely due to the constant production of neurotoxic and pro-inflammatory substances and a failure in endogenous control mechanisms (anti-inflammatories).

The treatments that delimit this process and reduce inflammation leading to the restoration of immunological balance, have shown to be effective in the control of seizure, especially in epileptic encephalopathies, where usually traditional pharmacological treatments show low effectiveness and clinical and functional deterioration of the patient are progressive.

Having follow-up and vigilance tools in patients with treated epilepsy gives us the opportunity of predicting

and detecting early complications, generating early therapeutic strategies that may prevent clinical deterioration of the patients and also have individualized management. Thus, further research dealing with biomarkers and the use of available knowledge in daily clinical practice, are necessary.

Conflicts of Interest

The authors declare no conflicts of interest.

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