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CRITICAL REVIEW

Factors not considered in the study of drug-resistant epilepsy: Drug-resistant epilepsy: Assessment of neuroinflammation

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Abstract

More than one-third of people with epilepsy develop drug-resistant epilepsy (DRE). Different hypotheses have been proposed to explain the origin of DRE. Accumulating evidence suggests the contribution of neuroinflammation, modifications in the integrity of the blood-brain barrier (BBB), and altered immune responses in the pathophysiology of DRE. The inflammatory response is mainly due to the increase of cytokines and related molecules; these molecules have neuromodulatory effects that contribute to hyperexcitability in neural networks that cause seizure generation. Some patients with DRE display the presence of autoantibodies in the serum and mainly cerebrospinal fluid. These patients are refractory to the different treatments with standard antiseizure medications (ASMs), and they could be responding well to immunomodulatory therapies. This observation emphasizes that the etiopathogenesis of DRE is involved with immunology responses and associated long-term events and chronic inflammation processes. Furthermore, multiple studies have shown that functional polymorphisms as risk factors are involved in inflammation processes. Several relevant polymorphisms could be considered risk factors involved in inflammation-related DRE such as receptor for advanced glycation end products (RAGE) and interleukin 1β (IL-1β). All these evidences sustained the hypothesis that the chronic inflammation process is associated with the DRE. However, the effect of the chronic inflammation process should be investigated in further clinical studies to promote the development of novel therapeutics useful in treatment of DRE.

KEYWORDS

blood-brain barrier, cytokines, drug-resistant epilepsy, neuroinflammation, polymorphisms

1 | INTRODUCTION

The World Health Organization estimates that at least 50 million people worldwide have epilepsy,[1] and one-third of these patients develop drug-resistant epilepsy (DRE).[2] The classic hallmark of DRE pathology is two or more antiepileptic drugs are being inadequate for seizure control.[3] There is an increase in sudden death by up to 50% in those with refractory epilepsy.[4] The lack of response in 30% of patients to pharmacological treatments has led to the proposal of several hypotheses to explain lack of response. The therapeutic target and transporter hypotheses are the most widely described theories of resistance to antiseizure medication (ASM). We will also mention other proposed hypotheses. The therapeutic target hypothesis emphasizes that sensitivity to treatment decreases due to alterations in the cellular targets of the drugs. For example, the α_2 subunit of the Na^+ channel, encoded by the SCN2A gene, is associated with resistance to ASMs.[5] The transporter hypothesis postulates that the drug resistance can be attributed to the overexpression of multidrug efflux transporters. P-glycoprotein (P-gp) is the most investigated efflux transporter, whose primary function is to maintain the integrity of the blood-brain barrier (BBB) by decreasing brain accumulation of drugs considered xenobiotics in the brain.[5]

Another critical hypothesis is the neural network hypothesis, which proposes that the loss of neurons results in a remodeling of the synaptic network. In this case, the brain's seizure control system is suppressed or inhibited, the brain's remodeling of the synaptic network, and is ineffective and drug access to the targets is restricted.[6] The intrinsic severity hypothesis suggests that high seizure rates before treatment are an important predictor of refractory epilepsy.[6] The genetic variant hypothesis states that polymorphisms are associated with pharmacodynamics, metabolic pathways, enzymes, ion channels, and neurotransmitter receptors and block drug binding, metabolism, and transport,[6] but neither of them thoroughly explains the neurobiological basis of this phenomenon.[6,7]

The mechanisms of refractory epilepsy are likely multifactorial, involving environmental, genetic, and disease- and drug-related factors.[8] Another factor to consider in this complex system is neuroinflammation. Recently, Löescher et al (2020) posited neuroinflammation and BBB dysfunction as potential mechanisms, because they are the primary hallmarks of human epileptogenic foci in various forms of DRE. Additionally, it has been described in animal models of acquired epilepsy.[3] It has been shown that the inflammatory process triggers hyperexcitability due to different cellular and molecular events.[6,7] However, information regarding inflammation and DRE is limited.

Key Points

- Inflammatory proteins are involved in the pathophysiology of seizures in patients with drug-resistant epilepsy.
- Seizure activity modifies the structure of the blood-brain barrier and activates inflammatory, oxidative stress, and efflux proteins such as P-gp.
- HMGB1 via Toll-like receptor (TLR) pathway triggers inflammatory responses and plays an important role in epilepsy
- Genetic studies in DRE have shown a weak relationship between inflammation and DRE in different ethnic groups.

This review provides recent information on the basic and clinical aspects of the role of inflammatory mediators and other activated molecules in DRE, which could be considered as a factor to support inflammation as an important component in DRE patients.

Neuroinflammation, a complex inflammatory response in the brain, is characterized by activation of the resident immune cell system, biosynthesis of inflammatory mediators, and release of related molecules in response to inflammatory challenge.[9-14] Recently, neuroinflammation has been considered to trigger epilepsy, epileptic seizures, and an inflammatory cascade response within the brain.[12,13]

Inflammatory responses in the central nervous system (CNS) have been differentiated into acute and chronic neuroinflammation. The acute neuroinflammatory response results in a phagocytic phenotype, activation of resident glial cells, release of inflammatory mediators such as reactive oxygen and nitrogen species, cytokines and chemokines, and the recruitment and infiltration of peripheral blood cells into the brain.[9,11] Conversely, chronic neuroinflammation is a long-standing inflammation in the CNS that implies the persistence of an inflammatory stimulus long after an initial injury or failure of the normal resolution mechanisms. Sustained release of inflammatory mediators implies increased oxidative stress, activation of microglia, promotion of cellular damage, and neurodegeneration.[15,16] Additionally, inflammatory processes are involved in a wide variety of diseases and conditions in the CNS.

On the other hand, several studies have provided evidence of the activation of innate and adaptive immune responses, primarily observed in brain biopsies of

patients with temporal lobe epilepsy (TLE).[17,18] This immune response can occur in response to factors that increase neuronal activity, as in the case of seizures. Thus, inflammatory mediators, such as cytokines, chemokines, and prostaglandins secreted by brain cells during epileptic activity, not only promote inflammation but also act as neuromodulators that affect neuronal function and increase excitability.[19] The pathological relevance of neuroinflammation is reinforced by the finding that it is a common feature of epilepsy in various drug-resistant forms with different etiologies and is not only related to autoimmune disorders or active CNS infections.[12,20-22] In addition, inflammatory mediators are endowed with CNS-specific neuromodulatory functions that may contribute to hyperexcitability and excitotoxicity.[23]

In addition, many other factors and patterns of refractoriness play critical roles in DRE and are likely to contribute to the complicated multifactorial pathology. Cumulative evidence from various studies has demonstrated that the pathogenesis of epilepsy is linked to neuroinflammation and cerebrovascular dysfunction.[8,24,25] Nevertheless, increasing evidence from clinical and experimental studies supports the idea that inflammatory pathways at the BBB might be associated with DRE.[2,26,27]

1.1 | Neuroinflammation and blood-brain barrier dysfunction in drug-resistant epilepsy

The BBB, a dynamic and complex interface between the circulating blood and the CNS, is established by brain endothelial cells closely associated with pericytes and astrocytic endfeet forming a neurovascular unit (NVU), surrounded by the basal lamina and organized by different extracellular matrix (ECM) proteins that are crucial for its establishment and integrity.[28-30]

Brain endothelial cells, characterized by a lack of fenestrae combined with low pinocytotic activity, are connected by tight junctions (TJs), which are the critical morphological component of the BBB.[28,30] These intercellular TJs (occludin, claudins, and junctional adhesion molecules) primarily exclude macromolecules such as proteins and small lipid-insoluble molecules from entering the brain.[31] These proteins are linked to the cytoskeleton by the zonula occludens family (ZO-1, ZO-2, and ZO-3).[28,32,33] These restrictive properties of the BBB due to tight junctions reduce the permeation of ions and other small hydrophilic solutes through the paracellular pathway. Thus, essential molecular flux must use predominantly transcellular bidirectional transport pathways, which may only enter via a series of membrane transporters (solute carriers, SLCs) and ATP-binding cassette (ABC) proteins and vesicular system transport.[30,34,35]

In particular, the ABC transporter family is a transmembrane protein superfamily that uses the energy released by adenosine triphosphate hydrolysis to transport various substrates through the cell membrane.[3,36,37] In the BBB, the multidrug resistance (MDR) gene encodes a family of proteins, including P-gp (ABCB1, MDR1), multidrug resistance-associated protein 1 (MRP1, ABCC1), and breast cancer resistance protein (BCRP), which are involved in the regulation of brain uptake and removal of toxic lipophilic metabolites into the blood.[3,36,37]

Chronic neuroinflammatory conditions may regulate the intracerebral expression of ABC transporters through several inflammatory signaling pathways. Overexpression of P-gp and MRP1 in epileptogenic brain tissue[38,39] and overexpression of MRP1 in dysplastic neurons, glia, and around intracerebral blood vessels in focal cortical dysplasia have been shown to cause refractory epilepsy.[25,40]

Likewise, much evidence has shown that neuroinflammation significantly contributes to the disruption and dysfunction of the BBB, triggering a chain of events leading to DRE.[3,8,25] Löscher et al[3] proposed three primary mechanisms for how inflammatory mediators may contribute to drug-resistant seizures: (i) induction of BBB dysfunction by promoting TJ disruption or induction of transcytosis, (ii) aberrant angiogenesis generating "leaky" vessels, and (iii) oxidative stress (Figure 1). Any changes in BBB permeability can promote the expression of inflammatory molecules by astrocytes. This vicious cycle contributes to recurrent seizures, cell loss, and maladaptive plasticity of the neuronal network, contributing to the intrinsic severity of the disease.[3]

Bazhanova et al[41] are in agreement with these mechanisms involved in DRE through inflammatory mediators. Additionally, they mentioned that lack of BBB functional integrity increases permeability and the direct consequences include penetration of albumin and neuroinflammatory molecules that affect the drug binding. This mechanism supports the stimulation of P-gp activity by proinflammatory mediators. In fact, activation of cytokine receptors on neurons rapidly alters their excitability through post-translational modifications of voltage-gated or receptor-coupled ion channels, inducing presynaptic changes in neurotransmission. A peculiar feature of these alterations is their rapid onset (seconds/minutes) and their long-term persistence in vivo (hours/weeks).[42] Upon activation of receptor-mediated pathways on neurons, these molecules induce extensive neuromodulatory effects that are distinct from their canonical activation of immune functions, and the neuromodulatory actions of some inflammatory molecules such as tumor necrosis factor alpha (TNF-α) contribute to the hyperexcitability

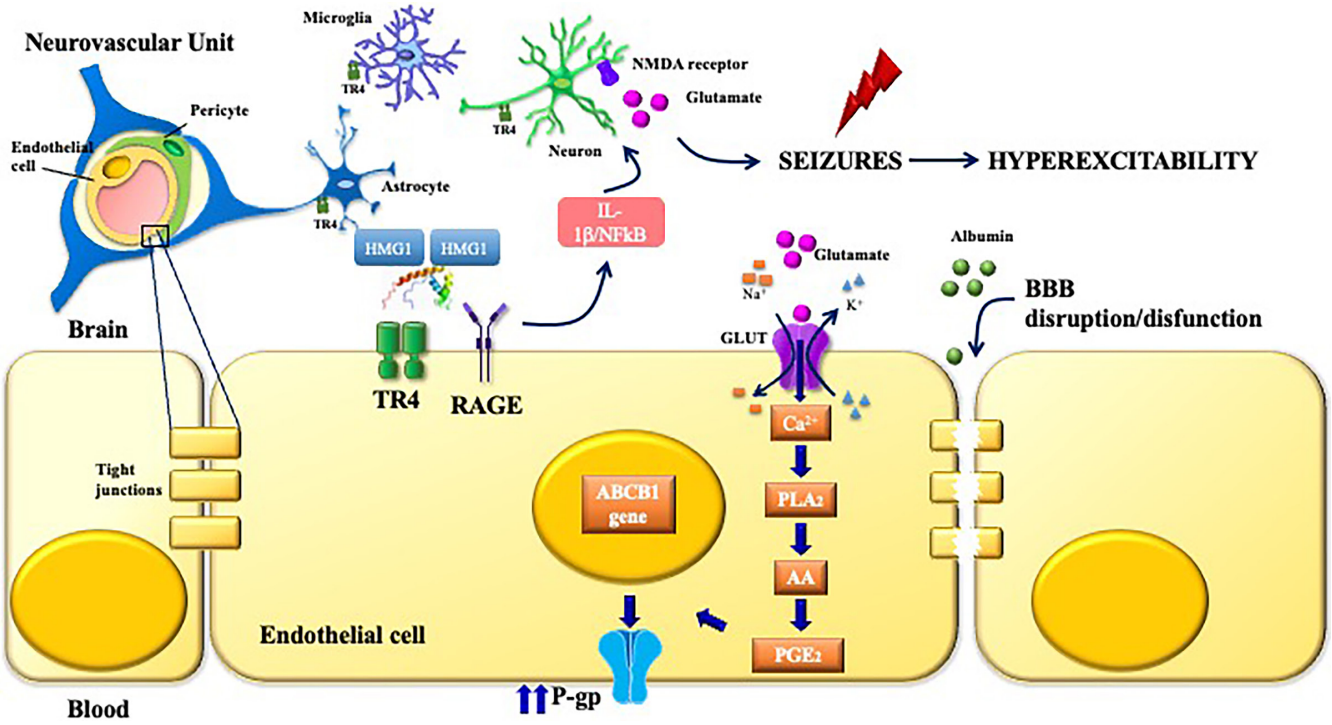

FIGURE 1 Potential mechanisms related to drug-resistant epilepsy. The blood-brain barrier (BBB) at the brain endothelial cells is the essential structure interface that regulates a bidirectional exchange of inflammatory cells and inflammation process in pharmacoresistant epilepsy. The neurovascular unit includes endothelial cell, pericyte, and endfeet astrocyte. HMGB1 is actively released by neurons, microglia and glia, and activates Toll-like receptor 4 (TLR4) and the receptor for advance glycation end products (RAGE), mediating pro-inflammatory activities on target cells. Therefore, there is an increased expression of pro-inflammatory molecules interleukin IL-1β (IL-1β) and nuclear factor kappa light chain enhancer of activated B cells (NFkB). IL-1β and NFkB rapidly enhances seizure generation. Neuroinflammation signaling activation results in brain vessels in areas of serum albumin extravasation which denotes BBB dysfunction. The influx of Ca^{2+} activates the phospholipase A2 (PLA2), catalyzing the arachidonic acid (AA) pathway, and synthesizes prostaglandin E2 (PGE2) by cyclooxygenase-2 (COX-2). Receptors of the nuclear membrane are stimulating, where the transcription of the ABCB1 gene that synthesizes P-glycoprotein (P-gp) in response to excessive glutamate is released by recurrent epileptic activity

of the neuronal networks underlying seizures.[43-45] For instance, interleukin-1β (IL-1β), endogenous nucleoprotein high mobility group box protein 1 (HMGB1) and TNF-α affect seizure susceptibility, a fact demonstrated in animal models, as shown by pharmacological interventions that mimic cytokine action or block TNFR1 (p55) or TNFR2 (p75) receptor signaling.[46-48]

Furthermore, TNF-α can induce neuronal channelopathies by affecting both the assembly and synaptic clustering of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors as well as neuronal membrane expression of GABA-A receptors. In particular, TNF-α induces the expression of GLUR2 receptors lacking Ca^{2+}-permeable AMPA receptors, a mechanism implicated in excitotoxicity and synaptic scaling.[49-51] TNF-α also promotes the induction of neuronal NMDA-NR1 receptors[52] and endocytosis of GABA-A receptors, decreasing inhibitory activity and enhancing excitability.[50] Activation of protein kinases, such as phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC), mediates TNF-α and IL-1β modifications in the function of ion channel and voltage-activated receptors in neurons.[17]

In addition to the rapid effects on neuronal excitability described above, which are mediated by post-translational modifications in neuronal channels, a transient increase in IL-1β and TNF-α in microglial cells resident in seizure-prone brain areas can induce long-lasting and profound synaptic changes in the brain. This chain of events contributes to the generation and establishment of a hyperexcitable neuronal network that contributes to seizure mechanisms, the neuropathology of epilepsy and likely drug resistance.[10,17,42,53,54]

Experimental evidence supports a link related with the neuroinflammatory process and P-gp induction, such as cyclooxygenase-1 and -2 (COX-1, COX-2), inducible forms of the enzyme that catalyzes the first step in prostanoid synthesis. It has been reported that P-gp regulation is dependent on COX-2 activity in rat brain capillaries.[55] The highly selective COX-2 inhibitors, SC-58236 and NS-398, decrease P-gp expression in the parahippocampal cortex

and ventral hippocampus.[15] In another report, the authors measured COX-1 and COX-2 expression in microglia, astrocytes, and neurons from patients with drug-resistant mesial temporal lobe epilepsy (MTLE) brain tissue. They found that COX-1 was expressed in microglia, and COX-2 was expressed in microglia and neurons.[48] In this regard, celecoxib, a COX-2 inhibitor, reduces seizure frequency and severity and prevents increased expression of P-gp in animal models of MTLE.[56] These results recognize COX as a critical factor in the transcriptional activation of the gene encoding P-gp in the epileptic brain.[55] The EP1 receptor (EP1R) for PGE2 appears to be a key factor mediating COX-2-induced P-gp upregulation. Indeed, increased P-gp in the hippocampus of a rat model of SE was excluded in animals treated with an EP1R antagonist, despite the aroused seizures.[57]

An important proinflammatory mediator, HMGB1 is an abundant nonhistone DNA-binding protein that regulates the transcriptional activity of genes and the maintenance of nucleosome structure.[58,59] HMGB1 is considered a representative damage-associated molecular pattern (DAMP), because it consists of molecules that are released upon cellular stress or tissue injury, that generate inflammatory responses by activating the innate immune system. HMGB1 is released extracellularly from different types of brain cells, including neurons and glia, under different stress conditions, such as hypoxia, ischemia, and cytokine stimulation as sensor molecule that responds to a diverse range of stimuli.[60-63] Orchestrating the inflammatory and immune response, HMGB1 promotes the pathophysiology of many CNS diseases, such as epilepsy (Figure 1).

After being released into the extracellular space, HMGB1 stimulates multiple receptors, including advanced glycation end products (RAGE) and Toll-like receptor 4 (TLR4).[64,65] In addition, HMGB1 binds IL-1α, IL-1β, C-X-C motif chemokine 12 (CXCL12), DNA, RNA, and lipopolysaccharide (LPS) when these molecules coexpress HMGB1, leading to increased activation of related receptors for each factor.[49] HMGB1 has also been reported to exhibit a chaperone-like function, whereby it transports LPS and nucleic acids into cells.[38] Similarly, HMGB1 has been characterized as a proinflammatory molecule and a key cytokine, because it activates inflammatory responses through multiple pathways by activating microglia and astrocytes, as well as disrupting of the BBB.[63,66] HMGB1 directly affects BBB cells, particularly endothelial cells and pericytes, which induce increased BBB permeability, that is inhibited by the neutralizing monoclonal antibody (mAb) which reduces the inflammatory responses and seizures by HMGB1[67,68] (Figure 1).

Nass et al (2020)[67] determined the plasma levels of HMGB1, MMP-9, and ICAM-1 after a single generalized convulsive seizure in epileptic patients. The authors observed a significant elevation of all these factors that suggest the presence of brain inflammation with BBB alteration, even after a single seizure that is marked by the release of MMP-9. Also, Kamaşak et al[69] observed a correlation between serum levels of HMGB-1, TLR4, IL-1β, IL-1R1, and TNF-α and the severity of epilepsy, and their data demonstrated that the serum levels of these cytokines were higher in cases of drug-refractory epilepsy. The authors note that signs of inflammation, neuronal damage, and transitory disruption of BBB following seizures underscore the widespread and likely detrimental effects of recurrent seizures on brain properties. HMGB1 might be involved in P-gp expression during status epilepticus, which is related to drug resistance.[70]

1.2 | Is inflammation a condition for drug-resistant epilepsy?

Evidence of brain inflammation has been observed in patients with DRE of various etiologies. Proinflammatory molecules, reactive astrocytosis, activated microglia, and other indicators of inflammation have been reported in hippocampal biopsies from TLE patients, around the tubercles in patients with tuberous sclerosis, and in some cases in biopsies from patients with epilepsy due to cortical dysplasia, which is a developmental disorder.[71-82]

These findings obtained in tissue from patients with TLE suggest specific inflammatory pathways that are chronically activated during epileptogenesis and persist in epileptic tissue, contributing to the etiopathogenesis of TLE.[82,83] In hippocampal biopsies from patients with drug-resistant TLE and hippocampal sclerosis (HS), microglial activation,[73,80] increased expression of proinflammatory molecules (IL-1, IL-6, and TNF-α), IL-1β, nuclear factor kappa light chain enhancer of activated B cells (NFkB) and complement receptor have been observed.[75,79] Similarly, systemic IL-6 levels in peripheral blood increase immediately after seizures and are long-lasting during the postictal period (24 hours after the ictal event) in patients with TLE, an effect that is not detected in patients with HS.[72] Expression of complement cascade proteins (C1q, C3c, and C3d) is increased within regions where neuronal cell loss occurs,[75] as well as in reactive astrocytes and microglia/macrophages.[71] These observations suggest the existence of a feedback loop between the proinflammatory cytokine system and components of the complement cascade, which may be critical for the propagation of the inflammatory response in TLE patients with HS. The functional implications of these findings are unknown but support the idea that inflammation may be intrinsic to the epileptogenic process and related to drug resistance.[13,78]

Elevated levels of proinflammatory cytokines have been detected, which are decreased in the serum of patients with drug-resistant temporal lobe epilepsy one year after surgical treatment compared to presurgical evaluation.[78] Serum levels of IL-1β and IL-6 after surgery in patients with DRE were decreased and associated with reduced seizures after surgery. This follow-up study was related to the clinical course of these patients in terms of the presence or absence of seizures one and two years after surgery. The decrease in IL-1β and IL-6 concentrations one year after surgery and the fact that most patients were seizure-free during this period supports the idea that seizures are the cause of the inflammatory disorders observed in patients with DRE. Evaluation of the involvement of inflammatory processes in DRE indicates that once the epileptogenic tissue associated with seizure reduction is resected, the observed inflammation disappears.[78] This finding supports the hypothesis that inflammation could primarily be a consequence of epileptogenic processes.

It has been proposed that anti-inflammatory treatments could be an additional therapeutic intervention in treating DRE in humans, especially in children with epileptic encephalopathies such as Rasmussen encephalitis (RE). These include broad-spectrum immunosuppressive steroids, human immunoglobulin, and immunosuppressive drugs such as rituximab a chimeric mouse-human monoclonal anti-CD20 antibody, which in some cases is combined with a ketogenic diet.[84] Many of these anti-inflammatory drugs clinically used for autoinflammatory and autoimmune diseases. Specific anti-inflammatory drugs that penetrate the brain with an acceptable safety profile could be tested for reuse in controlled clinical trials in drug-resistant epilepsies. Indeed, anti-inflammatory drugs are being used to treat drug-resistant focal epilepsies and in rare epileptic syndromes with encouraging results. For example, anakinra and canakinumab inhibit IL-1β, tocilizumab inhibits IL6, and adalimumab inhibits TNF-α. These treatments could be extended to epileptic encephalopathies,[85] refractory status epilepticus, or drug-resistant structural epilepsies suspected or known to be associated with brain inflammation,[86] but are not indicated to treat drug-resistant epilepsy, because not all cases of epilepsy. Nevertheless, it has been observed that these anti-inflammatory treatments (Table 1) temporarily improve the control of seizures. These treatments could not be extended over a long period of time, because the patients may present adverse effects or not respond to treatment. Currently available data come from case reports and retrospective analyses of small series or registry data and include heterogeneous groups of patients.

In recent decades, autoantibodies have emerged as underlying causes of otherwise unexplained epilepsy, and a link between autoimmunity and epilepsy has been suggested.[76] In addition to the increased susceptibility to seizures caused by inflammation, a direct epileptogenic role has been recognized for many specific autoantibodies, mostly directed against neuronal cell surface antigens.[87] The International League Against Epilepsy (ILAE) introduced the new concept of "epilepsy of immune etiology" to refer to patients whose epilepsy “is the direct result of an immune disorder in which seizures are a central symptom.”[88] The basis of the relationship between epilepsy and neuroinflammation has been studied in the context of RE for many years. Recently, it has been reported that epilepsy is caused by antibody-mediated conditions such as N-methyl-D-aspartate receptor (NMDAR) encephalitis and disorders triggered by innate immunity for instance febrile infection-related epileptic syndrome (FIRES). An increase in inflammatory markers has been observed in infantile spasms, suggesting that neuroinflammation plays a role in the development or propagation of certain epileptic syndromes previously thought to be solely of genetic etiology.[89]

Autoimmune encephalitis (AIE) is a group of brain disorders and inflammation caused by antibodies against neuronal receptors and cell surface proteins involved in neuronal excitability The pathophysiology of autoimmune encephalitis can be explained by antibodies against the NMDA receptor that target the NR1 subunit and cause selective cross-linking and internalization of NMDA receptors, leading to reduce of NMDA-mediated synaptic currents. Unlike T cell–mediated processes, this does not lead to cell death, and the effects can be reversed once the antibody is no longer present.[90] It is accepted that the appearance of these antibodies is likely a secondary pathological process of this disease and not a central element of the pathogenesis of autoimmune disease (AID). At present, the antibody theory does not seem to explain the pathogenic process.

Moreover, cellular immune mechanisms are implicated in these cases of encephalitis. Recent studies have primarily focused on the role of cytotoxic T cells in the pathogenesis of Rasmussen disease (RD). Pathological examination of the affected cerebral hemisphere revealed that cytotoxic CD8+ T cells occupy the majority of infiltrating T cells and, more importantly, that in inflammatory lesions, approximately 10% are granzyme B-positive CD8+ T cells. T cells gravitating to the neuronal membrane exhibit characteristics of cytotoxic granules,[91] which are associated with neuronal death and seizure induction.[92] The expansion of CD8+ T cell clones in the peripheral blood was related to disease severity in RD, so restricting the infiltration of these cells into the brain was considered a likely way to improve symptoms.[93]

Cohort studies have shown that 11% to 20.5% of patients with epilepsy of unknown etiology tested positive for specific antibodies.[94-96] As a consequence of the continuous

TABLE 1 Therapeutic and side effects of target specific antiinflammatory treatments inepilepsy

Drug	Target	Clinical data			Therapeutic effects	Side effects	References
		Number/ gender	Median age, years old (range, years)	Diagnosis			
Anakinra	IL-1R1	1 Female	2.7	FIRES	Significantly decrease in the frequency and duration of seizures	Not-reported	111
		1 Female	21	FIRES	Complete remission of seizures with minimal residual effects	Not-reported	112
		1 Male	10	FIRES	Significant seizure control	Not-reported	113
Tocilizumab	IL-6R	4 F:2 M	24.5 (19-61)	Cryptogenic epilepsy	Cessation of SE	Leukopenia, pneumonia, and sepsis	114
		1 Male	34	SRSE	Cessation of SE	Septic shock with fever	115
		1 Female	Not-reported	NORSE	Periodic epileptiform discharges were resolved	Not-reported	116
Rituximab	B Cell, $CD20^{+}$	1 Female	34	Autoimmune encephalitis with epilepsy	Normalized EEG, resolution of psychosis and agitation, and return of cognition and personality	Not-reported	117
		1 Female	72	Autoimmune encephalitis with epilepsy	Seizure freedom with return of cognitive function	Not-reported	
		1 Male	19	Lambert–Eaton syndrome	Cessation of SE	Not-reported	
Adalimumab	TNF-α	7 F:4 M	6.5 (1.5-37)	Rasmussen's encephalitis	5/11 patients had significant decrease in the frequency of seizures. 3/5 patients had stabilization of functional deficit	Well tolerated without major side effects	118
Methylprednisolone	Immune system cells	7 F:8 M	6 (3-29)	PEE	Significant decrease in the frequency of seizures after first therapy	No major side effects in our study	119
		2 F	2.5 (1.6-3.3)	CD	Significant decrease in the frequency of seizures after first therapy	No major side effects in our study	
Ibuprofen	COX2	111 Children, both genders	1-4	Febrile seizure	No significant differences were observed compared to the placebo group	Not-reported	120

TABLE 1 (Continued)

Drug	Target	Clinical data			Therapeutic effects	Side effects	References
		Number/ gender	Median age, years old (range, years)	Diagnosis			
Diclofenac	COX1	34 Children, both genders	1.7 (0.4-3.9)	Febrile seizure	Ineffective for the prevention of recurrences of febrile seizures	Not-reported	[121]

Abbreviations: CD, Cortical dysplasia; F, Female; FIRES, Febrile infection-related epilepsy syndrome; M, Male; NORSE, New-onset refractory status epilepticus; PEE, postencephalitis/encephalopathy epilepsy; SE, Status epilepticus; SRSE, Super-refractory status epilepticus.

discovery of autoantibodies related to epileptic symptoms, the antibody screening panel used in this context has progressively increased in the last two decades, thus making the comparison of the results of different studies more complicated. A great diversity of neuronal and glial proteins has been suggested, making the diagnosis more difficult. Several parameters have been considered, including the response to immunotherapy, imaging studies, clinical symptoms, and refractory seizures.[95] Much remains to be learned about this condition, which should be considered one of the hypotheses for refractory epilepsy.

These results all highlight the need for further research on the role of inflammation and the immune response in the CNS, particularly in DRE, to gain an understanding of the mechanisms in this clinical entity and to identify new immunomodulatory treatments, particularly for those cases in which surgery is not a therapeutic alternative. Most of the work in the pathogenic area is dedicated to the activation of infiltrating CD8+ T cells and microglia to explore better non-surgical treatments. Immunotherapy, including tacrolimus and adalimumab treatment, appears to be effective in the early phase of the disease in some cases. However, use of these pharmacological treatments, mentioned previously (Table 1), regulates the immune response, but they are not recognized as definite anticonvulsant treatments. The reports yielded partial and inconclusive results.

Inflammation should be considered a therapeutic target, resolving inflammatory processes in the brain, raises the threshold of hyperexcitability, decreasing the likelihood of seizure recurrence, hopefully providing a means of disease modification rather than mere symptomatic seizure control.[53]

1.3 | Are genetic variants in key inflammatory molecules associated with drug-resistant epilepsy?

Reports of genetic factors related to the immune system have been achieved due to the identification of clinical manifestations in patients with DRE (eg, autoimmune encephalitis)[90] or adverse drug effects (eg, toxic epidermal necrolysis).[97]

In epilepsy, the most robust genetic variability studies in DRE patients are those that have associated carbamazepine (CBZ)-induced hypersensitivity reactions due to the presence of genetic variants in the HLA gene in different populations. CBZ-induced hypersensitivity reactions appear to be immunologically mediated through an interaction of the drug or a drug-related compound with major histocompatibility complex (MHC) immune receptors leading to stimulation of immune cells such as

T lymphocytes and eosinophilic granulocytes.[98] In Asian populations from China and Malaysia, an association of CBZ-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (SJS/TEN) with the HLA-B*1502 polymorphism has been demonstrated.[99,100] In another population with ancestral European and Japanese lineages, the HLA-A*1301 allele presented an association with drug resistance to CBZ92.[99]

Other studies have attempted to identify a relationship between polymorphisms of inflammatory molecules and the development of DRE, but the results are controversial or questionable, since no other similar studies have been reported in these or other populations. Kanemoto et al[101] associated polymorphisms in the IL-1B (−500, +13953), IL-1A (−889), and IL-1RA (86 bp VNTR region in intron 2) genes with DRE. These authors determined that the −500 polymorphisms present in the promoter region of the IL-1B gene were significantly different among temporal lobe epilepsy with hippocampal sclerosis (TLE-HS+) patients and TLE without HS (TLE-HS−) in Japanese population. In a similar study performed in Chinese patients, the authors did not observe significant differences in the IL-1B -500 polymorphism between TLE-HS+ and TLE-HS− groups.[102] The IL-1β cytokine is an essential mediator of the inflammatory response and is produced by activated macrophages and glial and neural cells as a proprotein and that is subsequently processed to its active form by caspase 1.

He et al[103] found that a chemokine C-C motif ligand 2 (CCL2) genetic polymorphism is associated with DRE. In this study, they reported that the rs1024611 AA genotype in the CCL2 gene was associated with a greater susceptibility to DRE in a Chinese pediatric population, consisting of 386 patients with controlled epilepsy and 98 patients with DRE.[103] CCL2 is a chemokine considered a potent chemoattractant of monocytes and macrophages that is expressed in the central nervous system in microglia, astrocytes, and some neurons.[104]

Other variants have been studied for instance RAGE, encoded by the AGER gene, which is a type I single-pass transmembrane protein member of the immunoglobulin superfamily of cell surface molecules to able to transduce the effects of advanced glycation end products (AGEs) to generate robust proinflammatory responses in many cell types. RAGE binding to the cell surface results in rapid and sustained cell activation through multiple intracellular signaling pathways, leading to the propagation of inflammatory responses through the nuclear factor kB (NF-kB) pathway.[105,106] Several polymorphic sites of the AGER gene have been identified, which may affect the expression or function of RAGE and the course of inflammation-related disease. The relevant functional polymorphisms of RAGE were analyzed in a case-control study in an Asian population. A total of 274 healthy adults and 280 adult patients with epilepsy (140 patients controlled epilepsy and 140 with DRE) were evaluated.[107] In this study, the results were analyzed are included −429 C/T (rs1800625), −374 T/A (rs1800624), and G82S (rs2070600). They found that the homozygous and heterozygous (T/T + C/T) T allele of the genetic variant G82S (rs2070600) exhibited significant differences between healthy individuals and drug-resistant epileptic patients, identifying it as a risk factor for DRE.[107] The structural change of glycine to serine may display higher affinity for ligands, resulting in increased inflammatory mediators after RAGE activation.[108] This polymorphism has also been identified in patients with multiple sclerosis and Alzheimer's disease, but significant differences were found only in the Chinese population.[109,110] Notably, this polymorphic change (C>T) is higher in East Asian populations than in African (0.0053), European (0.0517), American (0.016), or South Asian (0.074) populations. Therefore, differences are associated with population characteristics rather than with the disease.

Therefore, evidence shows that only in some cases, the genetic variants in molecules of the immune system, directly or indirectly related to resistance to antiepileptic drugs, be considered in patients examining epilepsy. Studies should be performed in DRE patients with this type of association where the immune system is affected.

2 | CONCLUSIONS

Clinical and experimental data support the involvement of inflammation in the epileptic process, suggesting that specific inflammatory pathways are chronically activated in epileptogenic brain regions. Accumulating evidence suggests that inflammatory and immune reactions may play an important role in promoting increased neuronal excitability, thereby lowering the seizure threshold and promoting a chronic inflammatory state in the brain that is invariably associated with the involvement of various signaling pathways and primarily BBB damage. BBB dysfunction increases the severity of chronic epilepsy; due to the increase in P-gp in brain capillaries, and in cells near the vessels, such dysfunction also produced an increase in inflammatory mediators. The inflammatory molecules contributing to neuronal hyperexcitability induce enhanced seizure activity, which in turn produces excitotoxic damage to neurons and consequently changes neuronal networks, supporting the idea that neuroinflammation could be associated with the drug transporter and intrinsic severity hypothesis.

On the other hand, although that new drugs have been released and that, in some cases, target the immune

response and are effective, such as autoimmune encephalitis and some pediatric presentation syndromes, drug resistance remains unresolved. Therefore, it is necessary to continue working to investigate each of the hypotheses that have been described and integrate them, with the ultimate goal of developing more effective and comprehensive treatments for epilepsy, taking into account primarily the clinical factors, the history of the disease, the temporal response to drugs and inflammation as a factor that should be included in the new vision for the treatments.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia. 2010;51:883–90.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
3. Löscher W, Potschka H, Sisodiya SM, Vezzani A. Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. Pharmacol Rev. 2020;72:606–38.
4. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016;15:1075–88.
5. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365:919–26.
6. Tang F, Hartz AMS, Bauer BB. Drug-resistant epilepsy: multiple hypotheses, few answers. Front Neurol. 2017;8.
7. Rogawski MA, Johnson MR. Intrinsic severity as a determinant of antiepileptic drug refractoriness. Epilepsy Curr. 2008;8:127–30.
8. Sisodiya SM, Lin WR, Harding BN, Squier MV, Thom M. Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy. Brain. 2002;125:22–31.
9. Milatovic D, Zaja-Milatovic S, Breyer RM, Aschner M, Montine TJ. Neuroinflammation and oxidative injury in developmental neurotoxicity. In: Gupta RC, editor. Reproductive and Developmental Toxicology. 2nd ed. Cambridge, Massachusetts: Academic Press; 2017. pp. 1051–61.
10. Riazi K, Galic MA, Pittman QJ. Contributions of peripheral inflammation to seizure susceptibility: cytokines and brain excitability. Epilepsy Res. 2010;89:34–42.
11. Saavedra-López E, Casanova PV, Cribaro GP, Barcia C. In: Steiner H, Tseng KY, editors. Neuroinflammation in Movement Disorders. Handbook of Behavioral Neuroscience. Handbook of Behavioral Neuroscience, Amsterdam, Netherlands: Elsevier, 2016;Vol. 24: pp. 771–82.
12. Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia. 2005;46:1724–43.
13. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol. 2011;7:31–40.
14. Vezzani A, Friedman A, Dingledine RJ. The role of inflammation in epileptogenesis. Neuropharmacology. 2013;69:16–24.
15. van Vliet EA, Zibell G, Pekcec A, Schlichtiger J, Edelbroek PM, Holtman L, et al. COX-2 inhibition controls P-glycoprotein expression and promotes brain delivery of phenytoin in chronic epileptic rats. Neuropharmacology. 2010;58:404–12.
16. Vezzani A, Lang B, Aronica E. Immunity and inflammation in epilepsy. Cold Spring Harb Perspect Med. 2016;6(2):a022699.
17. Vezzani A, Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. Neuropharmacology. 2015;96:70–82.
18. Zattoni M, Mura ML, Deprez F, Schwendener RA, Engelhardt B, Frei K, et al. Brain infiltration of leukocytes contributes to the pathophysiology of temporal lobe epilepsy. J Neurosci. 2011;31:4037–50.
19. Orozco-Suarez S, Vega-García A, Feria-Romero I, Pizano-Torres ML, Rodríguez-Chavez E, Grijalva O. Autoimmune epilepsy: new development and future directions. In: Foyaca Sibat H, editor. Seizures; 2018. p. 13–32.
20. Jarrott B, Aprico K. Microglia: protective and pathogenic mediators. In: Kilpatrick TJRR, Ewsslingh S, editors. Inflammatory Diseases of the Nervous System. New York, NY: Cambridge University Press, 2010; p. 15–23.
21. Ravizza T, Vezzani A. Status epilepticus induces time-dependent neuronal and astrocytic expression of interleukin-1 receptor type I in the rat limbic system. Neuroscience. 2006;137:301–8.
22. Terrone G, Pauletti A, Pascente R, Vezzani A. Preventing epileptogenesis: a realistic goal? Pharmacol Res. 2016;110:96–100.
23. Kwan P, Li HM, Al-Jufairi E, Abdulla R, Gonzales M, Kaye AH, et al. Association between temporal lobe P-glycoprotein expression and seizure recurrence after surgery for pharmacoresistant temporal lobe epilepsy. Neurobiol Dis. 2010;39:192–7.
24. Contin M, Mohamed S, Santucci M, Lodi MAM, Russo E, Mecarelli O, et al. Cannabidiol in pharmacoresistant epilepsy: clinical pharmacokinetic data from an expanded access program. Front Pharmacol. 2021;12:637801.
25. Löscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nat Rev Neurosci. 2005;6:591–602.
26. Leclercq K, Matagne A, Provins L, Klitgaard H, Kaminski RM. Pharmacological profile of the novel antiepileptic drug candidate padsevonil: characterization in rodent seizure and epilepsy models. J Pharmacol Exp Ther. 2020;372:11–20.
27. West PJ, Saunders GW, Billingsley P, Smith MD, White HS, Metcalf CS, et al. Recurrent epileptiform discharges in the medial entorhinal cortex of kainate-treated rats are differentially sensitive to antiseizure drugs. Epilepsia. 2018;59:2035–48.
28. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. Neurobiol Dis. 2010;37:13–25.

29. Abbott NJ. Blood-brain barrier structure and function and the challenges for CNS drug delivery. J Inherit Metab Dis. 2013;36:437–49.
30. Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. Pharmacol Rev. 2005;57:173–85.
31. Liebner S, Dijkhuizen RM, Reiss Y, Plate KH, Agalliu D, Constantin G. Functional morphology of the blood-brain barrier in health and disease. Acta Neuropathol. 2018;135:311–36.
32. Daneman R, Pratt A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7:a020412.
33. Jones PM, George AM. The ABC transporter structure and mechanism: perspectives on recent research. Cell Mol Life Sci. 2004;61:682–99.
34. Campos-Bedolla P, Walter F, Veszelka S, Deli MA. Role of the blood-brain barrier in the nutrition of the central nervous system. Arch Med Res. 2014;45:610–38.
35. Löscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. NeuroRx. 2005;2:86–98.
36. Lazarowski A, Sevlever G, Taratuto A, Massaro M, Rabinowicz A. Tuberous sclerosis associated with MDR1 gene expression and drug-resistant epilepsy. Pediatr Neurol. 1999;21:731–4.
37. Sisodiya SM, Lin W, Squier MV, Thom M. Multidrug-resistance protein 1 in focal cortical dysplasia. Lancet. 2001;357:42–3.
38. Deng X, Xie Y, Chen Y. Effect of neuroinflammation on ABC transporters: possible contribution to refractory epilepsy. CNS Neurol Disord Drug Targets. 2018;17:728–35.
39. Stolp HB, Dziegielewska KM, Ek CJ, Habgood MD, Lane MA, Potter AM, et al. Breakdown of the blood-brain barrier to proteins in white matter of the developing brain following systemic inflammation. Cell Tissue Res. 2005;320:369–78.
40. Banks WA, Gray AM, Erickson MA, Salameh TS, Damodarasamy M, Sheibani N, et al. Lipopolysaccharide-induced blood-brain barrier disruption: roles of cyclooxygenase, oxidative stress, neuroinflammation, and elements of the neurovascular unit. J Neuroinflammation. 2015;12:223.
41. Bazhanova ED, Kozlovo A, Litovchenko AV. Mechanisms of drug resistance in the pathogenesis of epilepsy: role of neuroinflammation. A literature review. Brain Sci. 2021;11:663.
42. Galic MA, Riazzi K, Pittman QJ. Cytokines and brain excitability. Front Neuroendocrinol. 2012;33:116–25.
43. Pickering M, O'Connor JJ. Pro-inflammatory cytokines and their effects in the dentate gyrus. Prog Brain Res. 2007;163:339–54.
44. Vissing H, Aagaard L, Tommerup N, Boel E. Localization of the human gene for advanced glycosylation end product-specific receptor (AGER) to chromosome 6p21.3. Genomics. 1994;24:606–8.
45. Viviani B, Gardoni F, Marinovich M. Cytokines and neuronal ion channels in health and disease. Int Rev Neurobiol. 2007;82:247–63.
46. Balosso S, Maroso M, Sanchez-Alavez M, Ravizza T, Frasca A, Bartfai T, et al. A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta. Brain. 2008;131:3256–65.
47. Balosso S, Ravizza T, Aronica E, Vezzani A. The dual role of TNF-α and its receptors in seizures. Exp Neurol. 2013;247:267–71.
48. Weidner LD, Kannan P, Mitsios N, Kang SJ, Hall MD, Theodore WH, et al. The expression of inflammatory markers and their potential influence on efflux transporters in drug-resistant mesial temporal lobe epilepsy tissue. Epilepsia. 2018;59:1507–17.
49. Mollazadeh S, Sahebkar A, Hadizadeh F, Behravan J, Arabzadeh S. Structural and functional aspects of P-glycoprotein and its inhibitors. Life Sci. 2018;214:118–23.
50. Stellwagen D, Beattie EC, Seo JY, Malenka RC. Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-alpha. J Neurosci. 2005;25:3219–28.
51. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature. 2006;440:1054–9.
52. Wheeler D, Knapp E, Bandaru VV, Wang Y, Knorr D, Poirier C, et al. Tumor necrosis factor-alpha-induced neutral sphingomyelinase-2 modulates synaptic plasticity by controlling the membrane insertion of NMDA receptors. J Neurochem. 2009;109:1237–49.
53. Iori V, Frigerio F, Vezzani A. Modulation of neuronal excitability by immune mediators in epilepsy. Curr Opin Pharmacol. 2016;26:118–23.
54. Riazi K, Galic MA, Kentner AC, Reid AY, Sharkey KA, Pittman QJ. Microglia-dependent alteration of glutamatergic synaptic transmission and plasticity in the hippocampus during peripheral inflammation. J Neurosci. 2015;35:4942–52.
55. Bauer B, Hartz AM, Pekcec A, Toellner K, Miller DS, Potschka H. Seizure-induced up-regulation of P-glycoprotein at the blood-brain barrier through glutamate and cyclooxygenase-2 signaling. Mol Pharmacol. 2008;73:1444–53.
56. Schlichtiger J, Pekcec A, Bartmann H, Winter P, Fuest C, Soerensen J, et al. Celecoxib treatment restores pharmacosensitivity in a rat model of pharmacoresistant epilepsy. Br J Pharmacol. 2010;160:1062–71.
57. Pekcec A, Unkrüer B, Schlichtiger J, Soerensen J, Hartz AM, Bauer B, et al. Targeting prostaglandin E2 EP1 receptors prevents seizure-associated P-glycoprotein up-regulation. J Pharmacol Exp Ther. 2009;330(3):939–47.
58. Park JS, Aecaroli J, Yum HK, Yang H, Wang H, Yang KY, et al. Activation of gene expression in human neutrophils by high mobility group box 1 protein. Am J Physiol Cell Physiol. 2003;284:C870–9.
59. Stros M, Ozaki T, Bacikova A, Kageyama H, Nakagawara A. HMGB1 and HMGB2 cell-specifically down-regulate the p53- and p73-dependent sequence-specific transactivation from the human Bax gene promoter. J Biol Chem. 2002;277:7157–64.
60. Andersson U, Wang H, Palmblad K, Aveberger AC, Bloom O, Erlandsson-Harris H, et al. High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. J Exp Med. 2000;192:565–70.
61. Bonaldi T, Talamo F, Scaffidi P, Ferrera D, Porto A, Bachi A, et al. Monocytic cells hyperacetylate chromatin protein HMGB1 to redirect it towards secretion. EMBO J. 2003;22:5551–60.
62. Fiuza C, Bustin M, Talwar S, Tropea M, Gerstenberger E, Shelhamer JH, et al. Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. Blood. 2003;101:2652–60.
63. Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. Nat Rev Immunol. 2005;5:331–42.
64. Maroso M, Balosso S, Ravizza T, Liu J, Aronica E, Iyer AM, et al. Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. Nat Med. 2010;16:413–9.

65. Park JS, Gamboni-Robertson F, He Q, Svetkauskaite D, Kim JY, Strassheim D, et al. High mobility group box 1 protein interacts with multiple Toll-like receptors. Am J Physiol Cell Physiol. 2006;290:C917–24.
66. Yang H, Wang H, Czura CJ, Tracey KJ. The cytokine activity of HMGB1. J Leukoc Biol. 2005;78(1):1–8.
67. Nass RD, Wagner M, Surges R, Holdenrieder S. Time courses of HMGB1 and other inflammatory markers after generalized convulsive seizures. Epilepsy Res. 2020;162:106301. doi:10.1016/j.eplepsyres.2020.106301
68. Zhang J, Takahashi HK, Liu K, Wake H, Liu R, Maruo T, et al. Anti-high mobility group box-1 monoclonal antibody protects the blood-brain barrier from ischemia-induced disruption in rats. Stroke. 2011;42:1420–8.
69. Kamaşak T, Dilber B, Yaman SÖ, Durgut BD, Kurt T, Çoban E, et al. HMGB-1, TLR4, IL-1R1, TNF-α, and IL-1β: novel epilepsy markers? Epileptic Disord. 2020;22:189–93.
70. Wang F, Ji S, Wang M, Liu L, Li Q, Jiang F, et al. HMGB1 promoted P-glycoprotein at the blood-brain barrier in MCAO rats via TLR4/NF-κB signaling pathway. Eur J Pharmacol. 2020;880:173189.
71. Aronica E, Boer K, van Vliet EA, Redeker S, Baayen JC, Spliet WG, et al. Complement activation in experimental and human temporal lobe epilepsy. Neurobiol Dis. 2007;26:497–511.
72. Bauer S, Cepok S, Todorova-Rudolph A, Nowak M, Köller M, Lorenz R, et al. Etiology and site of temporal lobe epilepsy influence postictal cytokine release. Epilepsy Res. 2009;86:82–8.
73. Beach TG, Woodhurst WB, MacDonald DB, Jones MW. Reactive microglia in hippocampal sclerosis associated with human temporal lobe epilepsy. Neurosci Lett. 1995;191:27–30.
74. Boer K, Crino PB, Gorter JA, Nellist M, Jansen FE, Spliet WG, et al. Gene expression analysis of tuberous sclerosis complex cortical tubers reveals increased expression of adhesion and inflammatory factors. Brain Pathol. 2010;20(4):704–19.
75. Crespel A, Coubes P, Rousset MC, Brana C, Rougier A, Rondouin G, et al. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. Brain Res. 2002;952:159–69.
76. Geis C, Planagumà J, Carreño M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. J Clin Invest. 2019;129:926–40.
77. Iyer A, Zurolo E, Spliet WG, van Rijen PC, Baayen JC, Gorter JA, et al. Evaluation of the innate and adaptive immunity in type I and type II focal cortical dysplasias. Epilepsia. 2010;51:1763–73.
78. Lorigados Pedre L, Morales Chacón L, Pavón Fuentes N, Robinson Agramonte MLA, Serrano Sánchez T, Cruz-Xenes RM, et al. Follow-up of peripheral IL-1β and IL-6 and relation with apoptotic death in drug-resistant temporal lobe epilepsy patients submitted to surgery. Behav Sci. 2018;8(2):21.
79. Maldonado M, Baybis M, Newman D, Kolson DL, Chen W, McKhann G 2nd, et al. Expression of ICAM-1, TNF-alpha, NF kappa B, and MAP kinase in tubers of the tuberous sclerosis complex. Neurobiol Dis. 2003;14:279–90.
80. Morin-Brureau M, Milior G, Royer J, Chali F, Le Duigou C, Savary E, et al. Microglial phenotypes in the human epileptic temporal lobe. Brain. 2018;141:3343–60.
81. Ravizza T, Terrone G, Salamone A, Frigerio F, Balosso S, Antoine DJ, et al. High Mobility Group Box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy. Brain Behav Immun. 2018;72:14–21.
82. van Gassen KL, de Wit M, Koerkamp MJ, Rensen MG, van Rijen PC, Holstege FC, et al. Possible role of the innate immunity in temporal lobe epilepsy. Epilepsia. 2008;49:1055–65.
83. Ravizza T, Gafliardi B, Noé F, Boer K, Aronica E, Vezzani A. Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. Neurobiol Dis. 2008;29:142–60.
84. French JA, Koepp M, Naegelin Y, Vigevano F, Auvin S, Rho JM, et al. Clinical studies and anti-inflammatory mechanisms of treatments. Epilepsia. 2017;58:69–82.
85. Nabbout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. Lancet Neurol. 2011;10:99–108.
86. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol. 2019;15:459–72.
87. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. Physiol Rev. 2017;92:839–87.
88. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512–21.
89. Pardo CA, Nabbout R, Galanopoulou AS. Mechanisms of epileptogenesis in pediatric epileptic syndromes: Rasmussen encephalitis, infantile spasms, and febrile infection-related epilepsy syndrome (FIRES). Neurotherapeutics. 2014;11:297–310.
90. Iorio R, Assenza G, Tombini M, Colicchio G, Della Marca G, Benvenga A, et al. 25112548. The detection of neural autoantibodies in patients with antiepileptic-drug-resistant epilepsy predicts response to immunotherapy. Eur J Neurol. 2015;22:70–8.
91. Bien CG, Bauer J, Deckwerth TL, Wiendl H, Deckert M, Wiestler OD, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. Ann Neurol. 2002;51:311–8.
92. Bauer J, Elger C, Hans VH, Schramm J, Urbach H, Lassmann H, et al. Astrocytes are a specific immunological target in Rasmussen's encephalitis. Ann Neurol. 2007;62:67–80.
93. Schneider-Hohendorf T, Mohan H, Bien CG, Breuer J, Becker A, Görlich D, et al. CD8(+) T-cell pathogenicity in Rasmussen encephalitis elucidated by large-scale T-cell receptor sequencing. Nat Commun. 2016;7:11153.
94. Brenner T, Sills G, Hart Y, Howell S, Waters P, Brodie MJ, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia. 2013;54:1028–35.
95. Dubey D, Pittock S, McKeon A. Antibody prevalence in epilepsy and encephalopathy score: increased specificity and applicability. Epilepsia. 2019;60:367–9.
96. Husari KS, Dubey D. Autoimmune epilepsy. Neurotherapeutics. 2019;16:685–702.
97. Jamali S, Salzmann A, Perroud N, Ponsole-Lenfant M, Cillario J, Roll P, et al. Functional variant in complement C3 gene promoter and genetic susceptibility to temporal lobe epilepsy and febrile seizures. PLoS One. 2010;5:e12740.
98. Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01

genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55:496–506.
99. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. A marker for Stevens–Johnson syndrome. Nature. 2004;428:486.
100. Horta WG, Paradela E, Figueiredo A, Meira ID, Pereira VC, Rego CC, et al. Genetic association study of the HLA class II alleles DRB1, DQA1, and DQB1 in patients with pharmacoresistant temporal lobe epilepsy associated with mesial hippocampal sclerosis. Seizure. 2015;31:7–11.
101. Kanemoto K, Kawasaki J, Miyamoto T, Obayashi H, Nishimura M. Interleukin (IL)1beta, IL-1alpha, and IL-1 receptor antagonist gene polymorphisms in patients with temporal lobe epilepsy. Ann Neurol. 2000;47:571–4.
102. Jin L, Jia Y, Zhang B, Xu Q, Fan Y, Wu L, et al. Association analysis of a polymorphism of interleukin 1 beta (IL-1 beta) gene with temporal lobe epilepsy in a Chinese population. Epilepsia. 2003;44:1306-9.
103. He X, Li Y, Liu Z, Yue X, Zhao P, Hu J, et al. The association between CCL2 polymorphisms and drug-resistant epilepsy in Chinese children. Epileptic Disord. 2013;15:272–7.
104. Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res. 2009;29:313–26.
105. Hofmann MA, Drury S, Fu C, Qu WU, Taguchi A, Lu Y, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell. 1999;97:889–901.
106. Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, et al. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med. 2009;7:17.
107. Guo M, Wang J, Qi H, Liu F, Yao L, Zhang S, et al. Polymorphisms in the receptor for advanced glycation end products gene are associated with susceptibility to drug-resistant epilepsy. Neurosci Lett. 2016;619:137–41.
108. Jang Y, Kim JY, Kang SM, Kim JS, Chae JS, Kim OY, et al. Association of the Gly82Ser polymorphism in the receptor for advanced glycation end products (RAGE) gene with circulating levels of soluble RAGE and inflammatory markers in nondiabetic and nonobese Koreans. Metabolism. 2007;56:199–205.
109. Li K, Zhao B, Dai D, Yao S, Liang W, Yao L, et al. A functional p. 82G>S polymorphism in the RAGE gene is associated with multiple sclerosis in the Chinese population. Mult Scler. 2011;17:8.
110. Li K, Dai D, Zhao B, Yao L, Yao S, Wang B, et al. Association between the RAGE G82S polymorphism and Alzheimer's disease. J Neural Transm (Vienna). 2010;117:97–104.
111. Kenney-Jung DL, Vezzani A, Kahoud RJ, LaFrance-Corey RG, Ho ML, Muskardin TW, et al. Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol. 2016;80(6):939–45.
112. Westbrook C, Subramaniam T, Seagren RM, Tarula E, Co D, Furstenberg-Knauff M, et al. Febrile infection-related epilepsy syndrome treated successfully with Anakinra in a 21-year-old woman. WMJ. 2019;118(3):135–9.
113. Dilena R, Mauri E, Aronica E, Bernasconi P, Bana C, Cappelletti C, et al. Therapeutic effect of Anakinra in the relapsing chronic phase of febrile infection-related epilepsy syndrome. Epilepsia Open. 2019;4(2):344–50.
114. Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. Ann Neurol. 2018;84(6):940–5.
115. Vallecoccia MS, Martinotti A, Siddi C, Dominedò C, Cingolani E. Use of unconventional therapies in super-refractory status epilepticus: a case report and literature review. Clin EEG Neurosci. 2022;53(1):70–3.
116. Donnelly JP, Kasatwar N, Hafeez S, Seifi A, Gilbert A, Barthol C, et al. Resolution of cryptogenic new onset refractory status epilepticus with tocilizumab. Epilepsy Behav Rep. 2021;15:100431.
117. Kurukumbi M, Dave RH, Castillo J, Shah T, Lau J. Rituximab for autoimmune encephalitis with epilepsy. Case Rep Neurol Med. 2020;2020:5843089.
118. Lagarde S, Villeneuve N, Trébuchon A, Kaphan E, Lepine A, McGonigal A, et al. Anti-tumor necrosis factor alpha therapy (adalimumab) in Rasmussen's encephalitis: an open pilot study. Epilepsia. 2016;57(6):956–66.
119. Kimizu T, Takahashi Y, Oboshi T, Horino A, Omatsu H, Koike T, et al. Methylprednisolone pulse therapy in 31 patients with refractory epilepsy: a single-center retrospective analysis. Epilepsy Behav. 2020;109:107116.
120. van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW, Habbema JD, Moll HA. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. Pediatrics. 1998;102(5):E51.
121. Strengell T, Uhari M, Tarkka R, Uusimaa J, Alen R, Lautala P, et al. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Arch Pediatr Adolesc Med. 2009;163(9):799–804.

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