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Immune-mediated epilepsies

Tiziana Granata[*], **Helen Cross**[†], **William Theodore**[‡], and **Giuliano Avanzini**[§]
[*]Department of Child Neurology, Carlo Besta Neurological Institute, Milan, Italy
[†]UCL Institute of Child Health, Neurosciences Unit, London, United Kingdom
[‡]Clinical Epilepsy Section, National Institutes of Health, Bethesda, Maryland, U.S.A
[§]Department of Neurophysiology, Carlo Besta Neurological Institute, Milan, Italy

Summary

A pathogenic role of immunity in epilepsies has long been suggested based on observations of the efficacy of immune-modulating treatments and, more recently, by the finding of inflammation markers including autoantibodies in individuals with a number of epileptic disorders. Clinical and experimental data suggest that both innate and adaptive immunity may be involved in epilepsy. Innate immunity represents an immediate, nonspecific host response against pathogens via activation of resident brain immune cells and inflammatory mediators. These are hypothesized to contribute to seizures and epileptogenesis. Adaptive immunity employs activation of antigen-specific B and T lymphocytes or antibodies in the context of viral infections and autoimmune disorders. In this article we critically review the evidence for pathogenic roles of adaptive immune responses in several types of epilepsy, and discuss potential mechanisms and therapeutic targets. We highlight future directions for preclinical and clinical research that are required for improved diagnosis and treatment of immune-mediated epilepsies.

Keywords

Immune-mediated disease; Inflammation; Rasmussen's encephalitis; Infantile spasms; Temporal lobe epilepsy; Hemiconvulsion-hemiplegia

A pathogenic role of immunity in epilepsies has long been suggested based on observations of efficacy of immunomodulating treatments (namely steroids and immunoglobulin) and, more recently, by the finding of markers of inflammation and autoantibodies (auto-Abs) in a number of epileptic disorders. Clinical and experimental data suggest that both innate and adaptive immunity may be involved in epilepsy. The effector cells of adaptive immunity are antigen-specific B cells and T lymphocytes; these cells play major roles in activating inflammatory processes in response to viral infections and in autoimmune disorders. The innate immune system is the first line of defense against pathogens; it is activated by the nonspecific recognition of pathogens by immunocompetent cells (e.g., macrophages,

Address correspondence to Tiziana Granata, Department of Child Neurology, Carlo Besta Neurological Institute, Milan, Italy. granata@istituto-besta.it.

Additional Contributors

Jan Bauer, Vienna, Austria; Tallie Z. Baram, Irvine, CA, USA; Christian Bien, Bielefeld-Bethel, Germany; Olivier Dulac, Paris, France; Edouard Hirsch, Strasbourg, France; David Pearce, Sioux Falls, SD, U.S.A.

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granulocytes, natural killer cell) that express receptor binding to pathogen-associated molecular patterns. In the brain, innate immunity cell types comprise resident microglia, astrocytes, and neurons, which produce mediators of inflammation (e.g., cytokines). Increasing evidence suggests that innate immunity/inflammation activated in the absence of pathogens (i.e., sterile inflammation) contributes significantly to seizure activity (see also Friedman & Dingledine, this supplement).

In this article we review some types of epilepsy in which the pathogenic role of auto-Abs is strongly supported by clinical and biologic data (i.e., limbic encephalitides) and other types in which immune-mediated inflammation is demonstrated but the full pathogenic chain is still to be clarified (i.e., Rasmussen's encephalitis) or simply presumed (West and Landau-Kleffner syndromes). In addition, we discuss briefly the potential role of inflammation in degenerative diseases (e.g., Batten disease).

Rasmussen's Encephalitis (J. Bauer, Vienna, Austria)

Rasmussen's encephalitis (RE) is a rare, acquired devastating disease, which progressively affects one hemisphere (Bien et al., 2005). It was first described in 1958 by Theodore Rasmussen in a seminal paper that pointed out the peculiar clinical and pathologic characteristics, as well as etiologic and therapeutic issues (Rasmussen et al., 1958). It is characterized by a hemispheric brain inflammation resulting in unilateral brain atrophy; clinically there are drug-resistant focal seizures, worsening unilateral motor deficits, and cognitive decline. The etiopathogenesis of RE is still not fully understood, although it has been identified as a chronic inflammatory disease since its original description.

The initiating event of the inflammatory process in RE is unknown. A viral infection was originally proposed but not definitely demonstrated. In the 1990s, the possibility of antibody-mediated pathogenesis for RE was raised by the experiments on rabbits immunized with a recombinant fragment of the glutamate receptor GluR3 (Rogers et al., 1994), and was reinforced by the detection of antiGluR3 and other antibodies (Abs) directed against antigens of brain resident cells (namely, the presynaptic protein Munc18-1, *N*-methyl-$_D$-aspartate glutamate receptor (NMDA-type GluR) ε2 subunit [NMDA-GluRε2], and anti-alpha7 nicotinic acetylcholine receptors [α7nAChR]) in a subset of patients. In the following years, however, it became evident that the presence of circulating Abs could be secondary to the cerebral damage and that humoral immunity, albeit involved in RE, is not the primary actor. More recent evidence in fact strongly suggests the pivotal role of cell-mediated immunity, and relates the pathogenesis of RE to the cytotoxic T cells causing apoptotic cell death (Bien et al., 2002). The main pathologic features of RE are brain inflammation dominated by T cells, microglial activation, and microglial nodules, followed by neuronal loss and astrogliosis restricted to the affected hemisphere. Infiltrating T cells have been characterized as $CD8^+$ cells containing granules positive for granzyme B^+, and part of these cells were in close contact with major histocompatibility complex (MHC) class I-positive neurons. Granzyme B is a protease released by activated cytotoxic T cells into target cells that undergo apoptosis. This set of features is considered evidence of a cytotoxic T-cell attack against neuronal cells (Bien et al., 2002). More recently, the importance of astrocytes has been underlined by the observation of astrocytic apoptosis and loss within the cortex and the white matter. Indeed, Granzyme B^+ lymphocytes were found in close contact with astrocytes with granules polarized toward the astrocytic membranes, suggesting that astrocytes might be a target for T cells leading to astrocytic degeneration. The apoptotic astrocytes and astrocyte-deficient lesions were not present in other forms of epilepsy such as Ammon's horn sclerosis or focal cortical dysplasia, suggesting that T-cell–mediated death of astrocytes is a specific feature of RE. Considering their multiple functional roles, astrocyte degeneration might enhance neuronal loss as well as contribute to seizure induction and

maintenance (Bauer et al., 2007). Further evidence for an antigen-driven MHC class I–restricted T-cell attack against neurons and astrocytes has been proposed by the analysis of clonal composition and T-cell receptor repertoire of $CD4^+$ and $CD8^+$ T cells by means of CDR3 spectratyping and immunohistochemistry of peripheral blood and brain specimens from patients with RE (Schwab et al., 2009).

These recent findings recall the attention to the possibility that a viral antigen may act as the initiating event in the complex pathogenetic mechanism leading to the brain damage in RE. A cytotoxic T-cell response is in fact compatible with a viral infection, and a viral infection could explain the peculiar hemispheric distribution with centrifugal expansion observed in RE.

Previous studies failed to conclusively link a specific virus to RE, but this of course does not rule out the possible role of an unknown virus. To verify the viral hypothesis, Bauer and coworkers first searched for a general marker for virus-infected cells and identified it in the heat shock protein 70 (Hsp70). In vitro studies demonstrate that viruses use endogenous Hsp70 for their protein synthesis and that Hsp70 translocates in infected cells from the cytoplasm to the nucleus and colocalizes with viral inclusions. The value of Hsp70 as a marker of viral infection was confirmed by the analysis of paraffin-embedded samples taken from patients with various viral encephalitis (cytomegalovirus, herpes simplex virus, progressive multifocal leukoencephalopathy, human immunodeficiency virus) and from controls: the nuclear expression of Hsp70 was evident in most of the cases with viral encephalitis but only in 2 of 20 controls. The analysis of specimens taken from patients with RE revealed cells with nuclear expression of Hsp70 in 25 of 27 cases, and the presence of inclusion bodies in 19 of these 25 cases. Double staining with microtubule-associated proteins (MAP-2) for neurons and glial fibrillary acidic protein (GFAP) for astrocytes showed that Hsp70 could be found in both of these cell types. These findings suggest that RE rather than an autoimmune disease might be a form of viral encephalitis and that cytotoxic T cells are directed against a specific viral protein present in both neurons as well as astrocytes.

Future directions

Whether RE is due to an unknown virus, or to a common virus to which the RE patient reacts with an aberrant immune-mediated reaction needs to be elucidated. A direct pathogenic action of the virus itself should also be considered. Moreover, the type of inflammatory molecules produced by parenchymal brain cells or infiltrating leukocytes should be investigated.

Regarding therapy, antiinflammatory drug treatments should be determined by multicenter studies to control both the destructive brain process and the refractory seizures, before large resective surgery is required. Antiviral compounds may become a therapeutic option in the event of a proven viral cause of RE.

West Syndrome (Infantile Spasms; T. Z. Baram, Irvine, CA, U.S.A.)

West syndrome (WS), or infantile spasms, is an age-related epileptic encephalopathy with onset in the first year of life featuring clustered spasms and a chaotic electroencephalography (EEG) pattern known as hypsarrhythmia. It may occur in previously healthy children but occurs more frequently in infants with congenital or acquired neurologic problems and diseases. Independent of its etiology, WS mostly benefits from adrenocorticotropic (ACTH) and/or steroid treatment. Because ACTH and steroids have antiinflammatory properties, a potential inflammatory or immune-mediated pathogenesis for WS has been considered. However, direct evidence for a role of inflammation in WS is

minimal. Plasma and cerebrospinal fluid (CSF) levels of cytokines—including interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-α—have been studied in patients with WS, but the results are inconclusive (Liu et al., 2001; Tekgul et al., 2006; Haginoya et al., 2009). Findings of CSF reduced levels of IL-1ra (an anti-inflammatory cytokine that has been shown to act as an anticonvulsant in experimental settings) are consistent with an imbalance of proinflammatory and antiinflammatory molecules, which might play a role in the development of WS (Haginoya et al., 2009).

The mechanisms for WS and the role of immune and inflammatory processes might be elucidated by understanding the mechanisms by which ACTH and steroids suppress WS. These mechanisms are likely multiple and include direct effects on neuronal excitability, suppression of the levels of endogenous proconvulsant molecules including corticotropin-releasing hormone (CRH; Baram & Schultz, 1991) and antiinflammatory effects. The efficacy of ACTH and its superiority over steroids may be explained by its direct activation of the melanocortin receptors (MCRs; Brunson et al., 2001). MCRs function in several ways; in particular they suppress the endogenous convulsant CRH, a stress hormone expressed in numerous brain regions that appears to be elevated in brains of infants with WS (Baram et al., 1992; Brunson et al., 2002). The numerous etiologies of WS might share the fact that they “stress” the developing brain and thus elevate the brain levels of the stress hormone CRH. Importantly, MCRs inhibit nuclear factor-kB (NF-kB), a nuclear factor that induces the transcription of most of the molecules involved in inflammation, and potentially CRH. Inhibition of NF-kB and suppression of CRH might represent the interface of inflammation, stress, and epilepsy (Joëls & Baram, 2009).

Future directions

Further studies need to elucidate the specific role of MCRs in ictogenesis and epileptogenesis in West syndrome. Direct MCR agonists and drugs that inhibit NF-kB and suppress CRH should be identified and tested for their effectiveness and safety in the treatment of infantile spasms.

Landau-Kleffner Syndrome and Continuous Spike Waves during Sleep (E. Hirsch, Strasbourg, France)

Landau-Kleffner syndrome (LKS) and continuous spike-waves during sleep (CSWS), originally described as electric status epilepticus during sleep (ESES), are rare epileptic encephalopathies with typical onset in developmental age. They are both characterized by continuous EEG epileptic activity during sleep associated with neuropsychological disturbances. It is discussed whether they should be considered part of a clinical spectrum (Galanopoulou et al., 2000; Tassinari et al., 2000) and whether the pathogenesis should be related to the persistent convulsive discharge resulting in the “functional ablation” of cortical areas concerned with linguistic or other cognitive functions as originally suggested by Landau & Kleffner (1957). The LKS phenotype has been described in association with some cerebral disorders; however, in most cases no etiology can be found.

A role of autoimmunity in the etiopathogenesis of LKS has been suggested originally by Nevsímalová et al. (1992) based on the observation of a positive autoimmune reaction to central and peripheral myelin during the attacks of clinical worsening in four children with LKS. A significant improvement of speech function and autoimmune reaction during corticosteroid treatment was observed, suggesting a pathogenetic role of autoimmunity. Further support to an autoimmune pathogenic hypothesis was provided by the report of a consistent response after treatment with intravenous immunoglobulins (IVIGs) in an 8-year-old girl with LKS who failed other therapies (Fayad et al., 1997). The patient received three

courses of IVIGs, and after each one showed a dramatic diminution of the spikes in her serial EEGs that correlated with improved speech comprehension and expression. The improvement lasted 3 months after the first and second doses of IVIG and at least 16 months after the third dose. Noteworthy, the CSF immunoglobulin G (IgG)/protein ratio, which was increased before the initiation of IVIG therapy, lowered after treatment. This may indicate an abnormal immune response, which was reversed by IVIG therapy. The remarkable efficacy of IVIG on LKS was confirmed subsequently in a limited percentage of LKS patients (overall 3 of 15 treated patients) by the same group and by other investigators. Moreover several studies reported serum auto-Abs to brain-derived neurotrophic factor (BDNF) and to endothelial cells to be present in children with LKS with a frequency greater than healthy children (see references in Hirsch et al., 2006).

As for CSWS, several studies have shown the short-term efficacy of steroid therapy (up to 64%) to be higher than the efficacy of other agents. Of those, one third eventually relapsed and one fifth became steroid dependent. Immunoglobulins have been tested in only a limited number of cases of CSWS and found efficacious in 33%. Auto-Abs to brain components have been demonstrated in a limited number of patients with CSWS (see references in Hirsch et al., 2006).

Overall, several observations support the hypothesis that an autoimmune mechanism may play a role in the pathogenesis of epileptic encephalopathies included in LKS-CSWS spectrum.

Future directions

Multicenter studies should define the criteria by which a subgroup of patients can be identified with a demonstrated immunologic mechanism responding to immunomodulatory therapy.

Limbic Encephalitis and Neuroinflammation in Epilepsy: Potential Relationship to Ammon's Horn Sclerosis (C. Bien, Bielefeld-Bethel, Germany)

Limbic encephalitis (LE) is a syndrome known to occur in adults and recently also described in children and adolescents (Haberlandt et al., 2011). It is defined by recent-onset mediotemporal signs and symptoms (at least one of the following: disturbance of episodic memory, epileptic seizures of temporal semiology, or affective disturbances) plus at least one of the following features: diagnosis of a neoplasm; demonstration of a characteristic auto-Ab in the patient's serum or CSF (see below); a chronic lymphocytic–microglial encephalitis shown on histopathologic examination of a mediotemporal brain specimen; or, a mediotemporal fluid attenuated inversion recovery (FLAIR)–T_2-signal increase shown in an magnetic resonance imaging (MRI) scan that is not otherwise explainable. Temporal evolution from initial hippocampal swelling to atrophy may occur. In these cases, the affected hippocampi display MRI features of Ammon's horn sclerosis (AHS), and reveal segmental pyramidal cell loss and astrogliosis with accompanying signs of chronic encephalitis on histopathologic examination. More than 50% of patients with adult-onset mediotemporal lobe epilepsy (mTLE) had developed AHS as a consequence of LE (Bien et al., 2007).

Recently, it has become clear that auto-Abs in affected patients are important in making a definite diagnosis of LE and predicting prognosis. The most frequently accounted Abs in LE are directed to the voltage-gated potassium channel complex (VGKC) on the surface of neurons. The second most frequently found Ab in patients with LE is directed to the

intracellular enzyme glutamic acid decarboxylase (GAD). Onconeural Abs, which are directed to intracellular antigens (Hu, Ma, amphiphysin, CV2, Sox1), are the third most frequent Abs in LE if considered as one group. Further Abs associated with LE are directed against the *N*-methyl-$_D$-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or γ-aminobutyric acid $(GABA)_B$ receptors. For a summary with special relation to epilepsy, see the review article by Vincent et al. (2010). Recent work suggests that Abs to surface antigens predict a better prognosis under immunosuppressive treatment than Abs to intracellular antigens. Patients with anti-VGKC-Abs under monthly intravenous methylprednisolone pulses rapidly became seizure free and improved in terms of memory performance in parallel to a fall of VGKC antibody titers. In contrast to this, patients with anti-GAD-Abs took a chronic course with little clinical improvement and persistently elevated antibody concentrations (Malter et al., 2010).

The role of LE in other forms of mTLE

Is LE a “model” for other forms of mTLE? Inflammatory processes play a clear role in neurologic disorders such as multiple sclerosis. Several MRI techniques, such as magnetization transfer, gadolinium enhancement, diffusion-weighted imaging, and magnetic resonance spectroscopy (MRS) may be able to show aspects of active inflammatory processes (Rashid & Miller, 2008). In epilepsy, MRI has shown potential evidence for inflammation only in a few instances.

In children with prolonged febrile seizures, increased hippocampal T_2 signal intensity may be seen in the “acute” period within a few days after the episode. Some children develop evidence for AHS (Provenzale et al., 2008). It is uncertain how much of a role “inflammation” plays in this process. Other factors, such as excitotoxic injury, edema, and blood–brain barrier (BBB) breakdown may be also important, based on data derived from animal studies (see Friedman & Dingledine, this supplement).

Latent infection with a ubiquitous childhood virus, human herpesvirus-6 (HHV-6), associated with the common, self-limited childhood illness roseola infantum and febrile seizures, may play a role in mTLE (Theodore et al., 2008). In patients with immune compromise, reactivation may lead to severe limbic encephalitis. An ongoing multicenter study is investigating possible links between HHV-6 infection, febrile status epilepticus, and development of mesial temporal sclerosis (MTS). Investigation of temporal lobectomy specimens showed evidence of active HHV-6B, but not HHV-6A replication, in hippocampal astrocytes in about two thirds of patients with MTS, but not other causes of epilepsy.

Future directions

Determination of immunopathologic processes associated with distinct Abs and identification of the most effective treatments are future challenges. Early diagnosis and determination of antibody spectrum are important factors. Patients with clinical features suggestive of LE should undergo antibody testing and tumor search, adapted to the individual cancer risk. If neither antibody nor tumor is found, the diagnosis should be tentative. This stratification is important for meaningful subgroup-specific evaluation of natural history of the disease and treatment options.

The role of infections with common childhood viruses like HHV-6 and their reactivation during adulthood or upon immune dysfunction as triggers for AHS remain still to be elucidated. Identification of individuals at increased risk for the development of AHS as a consequence of a viral infection will also be important.

Hemiconvulsion–Hemiplegia Syndrome (O. Dulac, Paris, France)

Hemiconvulsion–hemiplegia syndrome (HHS), originally described by Gastaut, is a condition characterized by the occurrence of prolonged unilateral convulsions in the context of a febrile illness, in children younger than 4 years of age. This is followed by the development of an ipsilateral hemiplegia, persisting for at least one week. Later a focal epilepsy is often observed and hence the acronym hemiconvulsion–hemiplegia–epilepsy (HHE; Gastaut et al., 1960). Hemiconvulsion–hemiplegia syndrome was introduced as a syndrome in the first classification of the epilepsies reported by the International League Against Epilepsy (ILAE) in 1989 (Commission ILAE, 1989), and was included among the epilepsy syndromes and epilepsies in the most recent update of the classification (Berg et al., 2010). The apparent incidence of the syndrome has considerably decreased in developed countries over the last 20 years, possibly the result of the availability of benzodiazepines for emergency rescue treatment of prolonged seizures. There is some debate about whether hippocampal sclerosis following prolonged seizures may be a variant of the syndrome, but this is yet to be proven.

The etiology and pathophysiologic mechanisms underpinning the syndrome remain unclear; neuroradiologic studies have shown unilateral edematous swelling of the affected hemisphere at the time of initial status, followed by hemiatrophy independent of any vascular territory. Some advocate the presence of an underlying brain malformation and/or cortical dysplasia as a possible trigger for the events. Others have suggested that neuronal injury may be induced by venous thrombosis and/or cytotoxicity. Acute scanning in the periseizural state has shown abnormalities on diffusion-weighted imaging, suggesting cytotoxic edema of the seizing hemisphere (Freeman et al., 2002; Auvin et al., 2007). Neuropathologic studies have since suggested that edema is responsible for neuronal damage (Auvin et al., 2007). Notably cell death is not seen. To date acute infection or an antibody-mediated inflammatory process has not been implicated, although the trigger for such a prolonged seizure with resultant detrimental effects is unclear and a possible role for seizure-induced inflammatory pathways cannot be excluded (see Friedman & Dingledine, this supplement).

Future directions

The exact etiology and etiopathogenic mechanisms of HHE are still not fully understood. Therefore, the identification of children at risk for the disease and the therapeutic potential of antiinflammatory treatments remain to be elucidated.

Batten Disease (D. Pearce, Sioux Falls, SD, U.S.A.)

The juvenile onset form of Batten disease (JNCL) is the result of mutations in the *CLN3* gene (The International Batten Disease Consortium, 1995), but the underlying disease mechanisms remain poorly understood. *Cln3*-deficient mice are proving to be a valuable resource for investigating the consequences of *CLN3* mutation upon the central nervous system (CNS) (Mitchison et al., 1999), in that they display both pathologic and neurologic signs of the disorder including visual failure and motor coordination deficits (Weimer et al., 2006; Kovacs & Pearce, 2008).

Cln3-knockout mice have been shown to have an autoimmune response to GAD65, and the autoantibody to GAD65 binds to the brain protein resulting in inhibition of glutamic acid decarboxylase activity in the brain (Chattopadhyay et al., 2002). The GAD65 autoantibody has been demonstrated to be associated with astrocytic hypertrophy and a metabolic shift within the brain for the neurotransmitter glutamate. Furthermore, sera have been tested from individuals with Batten disease, and this testing has confirmed that all (approximately 50)

have a circulating autoantibody to GAD65. Further studies have revealed that there is evidence of the presence of additional autoreactive antibodies in Batten disease that clearly bind to neuronal antigens (Lim et al., 2006), indicating that it is likely that a general breakdown in autoimmunity to neuronal proteins exists. Evidence of IgG deposition and lymphocytic infiltration has been detailed subsequently in human and murine Batten disease. In addition, evidence for a size-selective breach in the BBB integrity in these mice suggests that systemically produced autoantibodies can access the CNS during disease progression and contribute to a progressive inflammatory response (Lim et al., 2007).

Both genetic and pharmaceutical approaches have been utilized to investigate the impact of the autoimmune response in *Cln3*$^{-/-}$ mice. The *Cln3*$^{-/-}$ mice were crossed with the B-cell deficient μ*MT* mouse (Kitamura et al., 1991), to generate mice that were immune deficient through the inability to produce B cells as well as lacking a functional CLN3 protein. These mice were incapable of generating endogenous IgGs. Importantly, *Cln3*$^{-/-}$ mice lacking B cells showed an amelioration in the characteristic deterioration of motor skills, which was attributed to an observed decrease in the inflammatory response as well as immune-mediated pathologies (Seehafer et al., 2010).

Mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase, an enzyme involved in the de novo pathway of purine synthesis in proliferating B and T lymphocytes, thereby attenuating any immune response. MMF was, therefore, used to treat *Cln3*$^{-/-}$ mice as a pharmacologic means to attenuate the immune response. Similar to the genetic ablation of B cells, a diminution was seen of both inflammatory response as well as immune-mediated pathologies. Remarkably this drug treatment also improved the motor function of *Cln3*$^{-/-}$ mice (Seehafer et al., 2010).

Future directions

A better understanding of the role of the *CLN3* mutation in the disease process is required. Moreover, the role of MMF in the treatment of children with Batten disease must be carefully explored and the risks of chronic immunosuppression weighted against its benefits. Therapeutic approaches may include other immunomodulating drugs currently available. The extent of the altered immune responses to neuronal proteins in Batten disease should be further evaluated. If this alteration is proven, one might wonder whether resetting of the immune system using human stem cell transplantation could be an experimental therapeutic option.

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