Epilepsy and Immune System: A Tour Around the Current Literature

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Abstract It is widely acknowledged that immune system influences several aspects of the central nervous system. Literature data have shown that immune system and autoimmune response play an important role in the pathogenesis of several neurodegenerative/neurological diseases (i.e Parkinson's and Alzheimer's Diseases, Multiple Sclerosis). However, very recent evidences of specific antibodies found in epileptic encephalitis, the good response to immune therapy in refractory epileptic syndromes and the strong relationship between systemic autoimmune disease and epilepsy suggest a plausible role for the immune system also in paroxysmal neurological disorders. In fact, an immune hypothesis represents a new way to approach epilepsy and could contribute to clarify several unanswered questions in the next future. In this review, we analysed these points mimicking a tour around current evidences from experimental animal models to clinical suggestions.

First Stop: Background

Although it is widely accepted that epilepsy can be defined as the persistent spontaneous tendency to generate seizure that underlies a persistent brain hyperexcitability, the exact physiopathology of epileptogenesis still remains unclear (Goldberg and Coulter 2013).

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Throughout the last few decades different hypotheses spanning from genetics to environmental or infective factors have been proposed to explain this latter phenomenon but unfortunately each attempt failed to give a unique and satisfactory explanation; even though the general knowledge has been widely improved (Goldberg and Coulter 2013).

Since 1977, several reports documented the efficacy of immunomodulating therapy (e.g. corticosteroids, immunoglobulin) in refractory epilepsy and based on this clinical observation a plausible immune origin has been postulated (Peachardre et al. 1977).

Currently, the recent findings of experimental studies have shown that the brain innate immunological cells such as microglia and astrocytes are able to produce cytokines and other mediators of inflammation contributing to seizure activity (Friedman and Dingledine 2011; Granata et al. 2011). These latest discoveries together with the detection of specific autoantibodies against channels or neuronal surface proteins in epileptic syndromes (Vincent et al. 2011b; Zuliani et al. 2012) and the intriguing findings that some mutated genes (LG1, KCNQ2-KCNQ3) are the cause of some types of epileptic syndromes have contributed to the immune theory as a plausible trigger or contributor of epilepsy.

In this article, we reviewed evidences for the immune system involvement in epilepsy, mostly focusing our attention on epilepsy syndromes strongly or suggestively linked to the immune system. We first describe what is our current knowledge obtained from experimental models, secondly from clinical studies showing a close relationship between the immune system and epilepsy.

Second Stop: Immunity Involvement in Experimental Models of Epilepsy

The role of immune activation in the generation of acute seizures and epilepsy has been investigated in animal models. While the role of inflammation during or after seizures in several models has been more systematically studied (Vezzani et al. 2011b, 2012), in comparison, only few studies have been pointed to the study of the immune system response and seizures following infections or the injection of LPS (Harvey and Boksa 2012). Some interesting results have been obtained studying seizures' generation in models of bacterial meningitis involving injection of group B streptococcus in infant rats (Kim et al. 1995; Kolarova et al. 2003) and models of viral CNS infection involving administration of Theiler's murine encephalomyelitis virus in young mice (Libbey and Fujinami 2011; Libbey et al. 2011). On the other hand, an enhancement in seizure susceptibility to convulsant drugs (e.g. lithium-pilocarpine, kainic acid) or an increase in seizure number and severity following LPS has also been characterized (Arican et al. 2006; Dmowska et al. 2010; Lee et al. 2000; Mirrione et al. 2010; Russo et al. 2013, 2014). Furthermore, several research groups provided evidence that, early in postnatal life, infection/immune activation can lead to long-lasting increased seizure susceptibility in adulthood.

Stewart et al. (Stewart et al. 2010) showed that young mice (P28–35) developed spontaneous epileptic seizures 2–7 months following injection of Theiler's murine encephalomyelitis virus. Similarly, Galic et al. (2009) have shown that intracerebroventricular injection of poly (I:C) in P14 rat pups increases seizure's susceptibility at adulthood; these data supports the concept that early exposure to either bacterial or viral immunogens can contribute or can be the cause of seizures and epilepsy also in adulthood.

Inflammation consists of the production of a cascade of inflammatory mediators, as well as anti-inflammatory molecules and other molecules induced to resolve inflammation, as a response to noxious stimuli (such as infection or injury), or immune stimulation, and is designed to defend the host against pathogenic threats (Vezzani et al. 2011b). The innate/adaptive immunity have been implicated in epilepsy; microglia, astrocytes and neurons are believed to contribute to the innate immunity-type processes causing brain's inflammation (Vezzani et al. 2011b). The activation of innate immunity and the transition to adaptive immunity are mediated by a large variety of inflammatory mediators, including cytokines-polypeptides, which play a pivotal role (Nguyen et al. 2002; Vezzani et al. 2011a, c). Cytokines are released by immunocompetent and endothelial cells, as well as by glia and neurons in the CNS, thereby enabling communication between effector and target cells during an immune challenge or tissue injury (Vezzani et al. 2011b). The most extensively studied are represented by IL-1beta, TNF-alpha and IL-6 (Friedman and Dingledine 2011). The major results in the field both support the concept that inflammation causes seizures or seizures cause neuroinflammation. Regarding the latter, several evidences have been reported regarding neuroinflammation-induction in the brain following single or prolonged seizures in various models in areas directly involved in seizure activity (Devinsky et al. 2013; Dhote et al. 2007; Foresti et al. 2011; Librizzi et al. 2012; Maroso et al. 2011; Ravizza et al. 2008; Reid et al. 2013). On the other hand, several studies support the role of inflammation in seizure generation (Auvin et al. 2007, 2009, 2010a, b, 2012; Galic et al. 2012; Marchi et al. 2012; Vezzani et al. 2008), even if it has recently been reported that LPS intrahippocampal infusion inhibits the development of kindling in rats (Ahmadi et al. 2013).

Neuronal hyperexcitability may be affected by cytokines in different ways (Silveira et al. 2012). IL-1beta contribute to excitotoxicity increasing calcium influx into neurons by N-methyl-D-aspartate (NMDA) receptors activation (Viviani et al. 2003), inhibiting glutamate reuptake by astrocytes (Hu et al. 2000). In addition, application of IL-1beta to hippocampal neurons results in the block of gamma-aminobutyric acid type A (GABAA) receptor function (Wang et al. 2000). Similarly, TNF-alpha has also been implicated in GABAA transmission decrease by endocytosis of its receptors in hippocampal pyramidal cells (Stellwagen et al. 2005). Neuroanatomic, imaging, neurochemical, and mechanistic approaches in vivo have been employed, and effector molecules of the cytokine have been described (Balosso et al. 2008; Friedman and Dingledine 2011; Maroso et al. 2010; Viviani et al. 2003). The involvement of TNF-alpha in programming neuronal excitability acutely and long term has also been examined (Riazi et al. 2010). Involvement of glutamate receptors in these TNF-alpha–mediated effects is suggested by the evidenced changes in

glutamate receptor subunit expression after LPS administration (Harre et al. 2008) as well as in TNF-alpha receptor subtypes knockout mice (Balosso et al. 2009), and by the ability of TNF-alpha to induce rapid changes in AMPA receptor subunit expression and function (Stellwagen et al. 2005). Finally, the recent involvement of mTOR pathway during epileptogenesis might also be considered as suggestive of an involvement of immune system (Russo et al. 2014). The role of the mTOR signaling pathway on the innate immune system and neuroinflammatory processes in the diseased brain has now begun to receive considerable attention (Maiese et al. 2013; Russo et al. 2013; Wang et al. 2013); this is despite the fact that the general immunomodulatory functions of mTOR have been widely studied, and rapamycin (RAP), a specific mTOR inhibitor, is a commonly used and successful immunosuppressant drug (Chi 2012). Recent findings support a specific interplay between neuroinflammation and mTOR pathway indicating the latter as a suitable target for the treatment of epilepsy and epileptogenesis (Curatolo and Moavero 2013; Liu et al. 2014; Russo et al. 2014).

Third Stop: Clinical Evidence of the Relationship Between Immune System and Epilepsy

Types of Epilepsy Strongly Linked with an Immune–Involvement

Rasmussen Encephalitis

The first evidence of fascinating relationship between seizures and immune-system dates back to 1958 when Theodore Rasmussen described a case of encephalitis later called Rasmussen encephalitis (RE). RE is a dramatic rare acquired disease with unfavourable prognosis that is characterized by progressive focal cortical unilateral hemispheric atrophy. Epilepsy is one of main feature of RE, especially unilateral untreatable motor partial seizure is the first sign of RE and remains for all the course of disease. It's possible to identify three clinical phases in RE: initially a prodromal stage (mean duration 7.1 months) characterized by low seizure frequency and mild hemiparesis (this phase could be absent in several cases); secondly an acute stage (RE could present directly in this stage) (mean duration 8 months) identified by high rate of simple partial untreatable motor seizure called "epilepsia partialis continua" (Bien et al. 2005; Granata et al. 2003b) reported it in 56–92 % of subjects) plus the appearance of neurological signs as progressive cognitive deterioration, hemiparesis, hemiatrophia and aphasia (if the dominant hemisphere is involved); finally, a residual stage characterized by stable neurological deficits and seizures with a lower frequency compared to acute phase. The duration of each stage is correlated with the severity of destructive processes even if there is a high rate of variability for each case.

Recently, new scientific discoveries have been achieved leading to an expansion of RE's syndrome spectrum, modifying and completing previous concepts. In fact, despite RE was considered a childhood's disease, it is currently accepted that it could occur at all ages especially in adolescent and even in adult subjects (Gambardella et al. 2008). An adulthood onset of RE is usually less severe, tends not only to progress more slowly but also more likely to respond to immunologic treatment (Hart et al. 1997; Leach et al. 1999; McLachlan et al. 1993). Furthermore, the clinical manifestations of RE related to "epilepsia partialis continua" and movement disorders as hemidystonia and hemiathetosis are emerging as adjunctive signs of RE and it seems to correlate with atrophy of the head of caudate nucleus (Gambardella et al. 2008). This latter radiological finding in addition to a progressive mono-hemispheric focal cortical atrophy and grey/white matter T2/FLAIR hyperintensities are considered one of the diagnostic neuroimaging criteria to diagnose RE (Bien et al. 2005). There are also very few reports of bilateral RE usually showing the presence of an underlying dual pathology (for example RE plus low grade tumour, cortical dysplasia, tuberosis sclerosis) (Chinchilla et al. 1994; Firlik et al. 1999; McLachlan et al. 1993; Palmer et al. 1999; Tobias et al. 2003).

It is very well-known that an early surgical exclusion of the affected hemisphere played a major role in seizure treatment (Wennberg et al. 1997) however, clinical experiences suggested that a combinations of corticosteroids, apheresis and high-dose IV immunoglobulin immunomodulatory treatment could be considered in some selective cases (Granata et al. 2003a).

The only unsolved concern regards the possible immune genesis of RE. Neuropathological studies of RE showing the presence of inflammatory infiltrates of T cells plus astrogliosis, suggest an involvement of adaptive part of immune system in RE disease (Bauer et al. 2007). In fact, histopathological-immunohistochemical studies on RE brain have shown that T lymphocytes not only are the main pathologic features of disease but are involved in neuronal death and damage through an apoptosis phase due to the release of granzyme B (Bien et al. 2002). The reasons for this attack against neurons and microglia activated by T lymphocytes is still unknown and needs to be clarified even if a viral hypothesis could be suggested but never definitely demonstrate.

Additionally, in 1990s the evidence in RE patients' serum of antibodies against glutamate receptor 3 (GluR3) has been pointed out as the possible cause for neuronal death through a damage mediated by antibodies or complement (Saiz et al. 2008).

Conversely, other studies have demonstrated that GluR3 antibodies are not present in all RE patients and are not specific of RE being observed in other epileptic syndromes, too (Mantegazza et al. 2002; Watson et al. 2004; Wiendl et al. 2001)

Limbic Encephalitis "neuronal surface antibodies syndrome"

Since upon the first description of Corsellis and colleagues (1968) limbic encephalitis (LE) was considered a rare paraneoplastic disorder with poor prognosis. The

underlying immune-mediated pathogenesis was identified in a cytotoxic response of T cell induced by onco-neuronal antibodies against intracellular antigens (Tuzun and Dalmau 2007). The disorder is characterized by a subacute onset of episodic memory loss, disorientation and behavioural changes associated with seizures, hallucinations, sleep disturbance. Neuroimaging usually shows signal changes in T2-weighted images, FLAIR sequences or diffusion in medial temporal lobe (Asztely and Kumlien 2012). It is becoming frequent the evidence that LE is not a classical onco-neuronal disorder but is associated with antibodies binding cell surface called "neuronal surface antibodies" (NSAbs) (Zuliani et al. 2012). This new entity is clinically similar to paraneoplastic LE with an important exception, namely the prognosis is favourable. In fact, these types of LE respond so well to immunotherapy to determine a substantial complete recovery (Vincent et al. 2011a). Although the incidence of this disorder is not well-established, current data seems to suggest that is more frequent than all encephalitis associated with paraneoplastic antibodies (Lancaster et al. 2011).

VGKC Complex Encephalitis

This represents a new fascinating chapter where the representative form is the LE associated to antibodies against voltage gated potassium channel complex (VGKC-Ab). Vincent et al. described a series of cases as a potentially reversible form of limbic encephalitis responsive to immunotherapy. Clinical and neuropsychological features of patients with VGKC-Ab are characterized by a subacute amnesia (1–52 week), global impairment of memory with sparing general intellect, confusion, sleep disturbance, hypothermia and seizure that occur mainly in adulthood males. Typically, MRI studies revealed either unilateral or bilateral change of signal in medial temporal lobes, especially on T2 or FLAIR weighted sequences, moreover this feature could be absent in 45 % of patients at onset (Irani et al. 2008).

In almost 80 % of cases, paraneoplastic screening (including paraneoplastic antibodies) is always negative and serum VGKC-Ab ranges from 450 to 5128 pM. These values decrease (from 2 to 88 % in comparison to basal level) after treatment with steroids, plasma exchange and intravenous immunoglobulin. The decrement of VGKC-Ab is correlated with improvement of neuropsychological performances and all symptoms are broadly revertible after immunotherapy (Vincent et al., 2004). This last point represents the substantial difference between VGCK syndrome and other untreatable rapidly progressive dementia conditions such as Creutzfeld-Jakob disease (Geschwind et al. 2008).

Previous reports postulated that VGKC complex belongs to two proteins: the leucine rich glioma inactivated 1 protein (LGI1) and contactin associated protein 2 (CASPR2), but nowadays the results of several investigators indicate that these are two diverse entities from VGKC (Irani et al. 2010; Lai et al. 2010).

LGI1 is a secreted neuronal protein highly expressed in hippocampus and neocortex that interacts with a presynaptic protein called ADAM23 and postsynaptic ADAM 22, modulating presynaptic Kv1 potassium channels (Lancaster et al. 2011).

Previously, genetic studies have demonstrated that LGI1 plays an important role in epilepsy field in fact mutations of LGI1 are responsible of some autosomal dominant partial epilepsy with auditory seizures indeed the studies performed on models of transgenic mouse have shown that LGI1 mutations increase the excitatory synaptic transmission modifying dendritic morphology (Nobile et al. 2009; Zhou et al. 2009).

Despite a common substrate, the clinical spectrum correlated to LGI1 mutation is different by LE with LGI1-Ab. In fact LE with LGI1Ab is characterized by an encephalitis rapidly progressive, with two peculiar findings: hyponatraemia and antiepileptic drug refractory facio-brachial dystonic seizures, in almost all cases without surface EEG ictal pattern but always reversible after immunotherapy (Irani et al. 2008).

NMDAR-Ab Encephalitis

A distinctive entity among LE field is the encephalitis N-methyl-D-aspartate-antibody related (NMDAR-Ab). The target of this syndrome is represented by NMDA receptors (NMDARs) which are ligand-gated cation channels involved in neuronal plasticity and synaptic transmission, widely expressed in the amygdala, thalamus, hippocampus and prefrontal cortex. It is known that the pathogenic mechanism of anti NMDAR antibodies is based by a selective and reversible reduction of density of NMDAR surface protein with a subsequent decrease of synaptic NMDAR-mediated current. It has been suggested that a reduction of NMDAR activity might promote epileptogenesis through an increase in glutamatergic activity (Dalmau et al. 2011).

The spectrum of LE NMDAR-Ab differs by other LE for demographic, clinical and instrumental findings. In fact, people affected by LE NMDAR-Ab is peculiar since it is mainly represented by children and young woman. The symptomatology profile is characterized by a prodromal phase presenting as viral illness followed by psychiatric disorders (including anxiety, behavioural changes and psychosis) thereafter followed by the occurrence of seizures, alteration of consciousness and dysautonomia. Sometimes autonomic disturbance may require admission to intensive care unit for central hypoventilation and a temporary pacemaker for cardiac rhythmic alterations (Sansing et al. 2007). Although the first descriptions of LE NMDAR-Ab was related to a ovaric teratoma, recent data showed that less than 5% of cases are related to tumours. This LE has a good response to immune-treatment including plasma exchange, steroids, intravenous immunoglobulin or combination. Some uncontrolled studies have suggested a second-line treatment with immunotherapy, ciclophosphamide, rituximab or both (Titulaer et al. 2013)

Forth Stop: Practical Evidence of Autoimmune Disease and Epilepsy

It is very well known how the incidence of seizures is very high in course of systemic autoimmune diseases (Vincent and Crino 2011).

Based on this, several authors have postulated that immune system might be involved in the pathogenesis of some forms of epilepsy and hyperexcitabilty. The forth stop of our tour will focus on autoimmune diseases that are strongly linked to seizures trying to give a key for understanding this close relationship.

Systemic Lupus Erythematous

Seizures occur in almost 10–20% of patients affected by systemic lupus erythematous (SLE) and the prevalence of epilepsy in these patients is eight times higher than general population. Furthermore, in a significant quote of patients (5–10%) seizures can precede the clinical onset of SLE of several years (Aarli 2000).

These seizures are mainly generalized while seizures occurring during SLE are either focal or generalized-tonic (Mackworth-Young and Hughes 1985).

An important prognostic factor in patients with a single epileptic seizure is the presence of antiphospholipid antibodies since they are correlated with a greater risk of developing new seizures (Peltola et al. 2000).

Several theories speculate that an immune-mediated damage of antinuclear antibodies that cross-react with neuronal antigens or an immune complex-mediated vasculitis could underlie epileptogenic mechanism in patients with SLE. On the other hand, there still is an important unanswered question: what is the meaning of increased level of antinuclear antibodies in patients with idiopathic epilepsy? Some authors reported that the use of antiepileptic drugs might responsible for the increment of antinuclear and antiphospholipid antibodies (Billiau et al. 2005). Although the real cause is almost unknown, epilepsy plays an important role in SLE representing one of the diagnostic criteria for its diagnosis.

Coeliac Disease

Coeliac disease (CD) is a chronic immune T cell-mediated disease against gluten and related proteins that occurs in individuals with a genetic predisposition. In the last years, an increasing number of reports have shown that CD is not only confined to gastrointestinal system, in fact other systems such as nervous system are involved in this disease. The association between CD and epilepsy is controversial and it ranges from 0.5 to 7.2% (Ruggieri et al. 2008; Zelnik et al. 2004), but a recent meta-analysis showed that paediatric population with CD has a 2.1 fold increased risk of developing epilepsy (Lionetti et al. 2010). On the other hand, some authors

reported in epileptic population a greater prevalence of CD (about 2–3 %) (Cronin et al. 1998; Emami et al. 2008; Labate et al. 2001). Recently, a population-based cohort analysis confirmed a moderate risk of epilepsy in individuals with CD reinforcing the potential role of immunologic pathogenesis in the development of epilepsy (Ludvigsson et al. 2012).

This role is also supported by the exposure to gliadin determining an immune response through the activation of T cell against transglutaminase (especially form 6 that is expressed mainly on cerebral cortex, amygdala, hippocampus, cerebellum) and the production of aggressive pro-inflammatory cytokines. Although temporal lobe epilepsy represents the most common type of epilepsy associated with CD, especially in patients with hippocampal sclerosis (Peltola et al. 2009), Labate et al. among other has reported a high rate of silent CD in partial epilepsy with occipital paroxysms, with and without cerebral calcifications and proposing a routine sierological screening of CD antibodies in this population. In fact, it is already accepted as indicator of silent or latent CD the positivity to antibodies to gliadin or transglutaminase in patients without signs of gastrointestinal involvement (Vincent and Crino 2011).

This condition is extremely common in adulthood, when CD is often asymptomatic and neurological illness, including epilepsy, is reported as the first sign preceding the diagnosis of CD (Maki and Collin 1997).

The correlation between seizure and gluten is demonstrated by the successful control of refractory seizures in patients with CD after a treatment with gluten-free diet (Harper et al. 2007; Mavroudi et al. 2005).

A recent study of Ranua et al. (Ranua et al. 2005)reported that the presence of CD antibodies did not differ between patients with epilepsy compared to control group, but the prevalence of antigliadin antibodies is higher in patients with primary generalized epilepsy, suggesting a genetic predisposition. However, several aspects remain obscure and further studies are needed to better clarify the link between immune system and epilepsy in CD patients.

Multiple Sclerosis

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system of unknown origin (Vincent and Crino 2011).

Seizures are considered part of MS spectrum and can occur in every phase of the disease either before or after the onset of MS but mainly during relapses. In the majority of cases, seizures appear after several years of MS onset and occasionally can be the unique presenting manifestation of MS (Gambardella et al. 2003; Trouillas and Courjon 1972).

Although the prevalence of epilepsy in MS is more common than in the general population (mean value is assessed about 2.3 %) the rate is extremely heterogeneous ranging from 0.5 to 10.8 % (Drake and Macrae 1961; Ghezzi et al. 1990; Kinnunen and Wikstrom 1986; Matthews 1962).

Each type of seizure have been reported in association with MS, however, secondary generalized tonic-clonic are the most frequent types of seizures (Sander et al. 1990; Striano et al. 2003).

Moreover, several studies reported the occurrence of uncommon forms of epilepsy associated to MS as sensory partial seizures, musicogenic epilepsy and aphasic status epilepticus in particular aphasia is been noted as a predominant symptom of seizure in MS.

Although seizures might occur at any time during the course and in every form of MS (primary or secondary progressive as well as relapsing-remitting), most typically, seizures appearing during relapses are self-limiting and do not generally require antiepileptic treatment.

Several hypotheses have been proposed regarding the pathogenic mechanism underlying epilepsy in MS. Some suggested that epileptogenesis is either sustained by oedema originated by active demyelinating lesions by pro-inflammatory cytokines such as tumour necrosis factor-α, specific interleukins that are produced by activation of microglia in MS lesions.

Hashimoto Encephalopathy

Since 1966, Hashimoto encephalopathy (HE) is considered a rare steroid-responsive treatable encephalopathy associated with autoimmune thyroiditis (Hashimoto thyroiditis)(Chong et al. 2003). HE has only a gender predilection (as other autoimmune diseases, it affects 4–5 times more females than males) but it is not age dependent. There are two clinical HE-correlated subtypes: a vasculitic-like pattern (acute or subacute multiple stroke-like episodes associated with focal neurological deficit and variable degrees of cognitive and consciousness dysfunction) and a diffuse gradual cognitive impairment with dementia, neuropsychiatric symptoms and impairment of consciousness (Afshari et al. 2012).

Seizures affect 66% of HE patients, especially in childhood when HE might be very insidious and it might be suspected when new onset unexplained deterioration is associated with refractory epilepsy (Berger et al. 2010; Vasconcellos et al. 1999).

Type of seizures reported in HE subject are focal or secondary generalized convulsions, whereas very rarely status epilepticus or absence status have been described (Ferlazzo et al. 2006; Vasconcellos et al. 1999). EEG findings are not specific and show a diffuse background slowing as reported in other encephalopathy (Chong et al. 2003; Kothbauer-Margreiter et al. 1996), a resolution of EEG pattern is correlated with clinical improvement (Henchey et al. 1995).

Brain imaging is not useful, in fact, half cases show normal MRI while the others show non specific alterations (Chong et al. 2003; Kothbauer-Margreiter et al. 1996).

Conversely, in 60–85% of subject with HE, elevated protein concentration and less commonly lymphocytic pleocytosis is present at CSF analysis. However, two are the hallmark features of HE: firstly the detection in serum of antithyroid antibodies (but is not specific in fact are positive in 10% of general population) independently of thyroid hormonal profile and the gravity of disease; secondly the rapid

and dramatic response to high–dose to steroid-treatment with a complete recovery within 2 months. The combination of these characteristics is distinctive and exclusive of HE and allows an easy differential diagnosis by other autoimmune forms of encephalitis. Disease relapse is possible after steroids' tapering, and in some cases, a combined immunomodulatory treatment with rituximab, cyclophosphamide, immunoglobulins and plasma exchange is necessary (Vincent and Crino 2011).

How antithyroid antibodies can trigger seizures and neurological manifestations still remains unclear. Post–mortem studies showed a lymphocyte infiltration around small vessels in brain parenchyma of HE patients, thus suggesting a microvascular inflammation damage for an immune complex deposition mediated by antithyroid antibodies (Duffey et al. 2003; Nolte et al. 2000).

Nevertheless, it is unknown the mechanism by which anti-thyroids antibodies can reverse neuronal and thyroid tissue damage, actually, it is not possible to exclude other antibodies or/and other mechanism underlying HE.

Fifth Stop: Practical Evidence of Probable Dysimmune Epilepsy

In these last years, there is a growing interest about catastrophic childhood epileptic encephalophaties, to prevent neurological complications and negative cognitive influences. To achieve these purposes, it is necessary to know the real underlying causes to establish a correct early clinical and therapeutic approach to obtain better outcomes. Based on the effectiveness of immunomodulatory treatments in these epilepsies (Eriksson et al. 2001; Lousa et al. 2000; Wiendl et al. 2001) a potential role of immunity in their pathogenesis is reasonable. In this stop we focus the attention on these severe epileptic syndromes.

West Syndrome

West syndrome (WS) is an infancy epileptic syndrome with onset in the first years of life characterized by brief tonic spasms, arrest or regression of psychomotor development and a chaotic pattern on electroencephalogram called as " hypsarrhythmia". Essentially, it is possible to distinguish two subgroups in WS: symptomatic (underlying a brain damage such as neonatal asphyxia, meningoencephalitis, cerebral dysgenesis, and congenital metabolic disorders) or cryptogenic, if occurred in previously healthy children *(International League Against Epilepsy Task Force, 1989)*.

Independently by subgroups of origin, the hallmark of WS is the responsiveness to immune suppressants therapy as adrenocorticotropic hormone (ACTH) or glucocorticoids, which is responsible of cessation of spasms in more than 90 % of patients (Kondo et al. 2005; Tsuji et al. 2007; Yamamoto et al. 2007).

Hence, an immune mechanism in the pathophysiology of WS is highly supported. Therefore, in order to clarify the immune pathophysiology of WS, several studies have faced the question, however, the profile of cytokine patterns produced by lymphocytes and other pro and anti-inflammatory molecules in plasma e CSF fluid of patients with WS were inconclusive (Haginoya et al. 2009; Liu et al. 2001).

Takashi Shiiharaa et al. (2010) studying peripheral blood lymphocyte subset and serum cytokine profiles have suggested that, in WS, T-cell and B-cell activation played a role and ACTH therapy may associate with T-cell inactivation, unfortunately these data were not confirmed by other reports. The efficacy of ACTH and the superiority to corticosteroids can be explained through a suppression of endogenous convulsant hormone CRH (highly expressed in WS brain) through a direct activation melanocortin receptor and a block of transcription of nuclear factor-kB (this factor is involved in inflammation and epileptogenesis)(Baram et al. 1992; Baram and Schultz 1991).

To date, even if conceivable, an immune mechanism in the pathophysiology of WS has been suggested, however, the exact mechanisms remain unknown and yet might be seriously investigated.

Landau-Kleffner Syndrome

Landau-Kleffner syndrome (LKS) is another rare developmental syndrome, characterized by acquired aphasia during early childhood epileptic seizures, behavioral problems, abnormal epileptic activity on EEG during sleep. Since the first description by Landau and Kleffner in 1957, several hypotheses were investigated to discover the pathogenesis, but of all only an immune pathologic cause seems to be more reliable. This theory was suggested by Mikati et al. and Lagae et al., following the observation of a significant improvement of language function and EEG abnormalities after treatment with corticosteroids and/or repeated IVIG infusions (Lagae et al. 1998; Mikati and Saab 2000)

Moreover Fayad et al. (1997) and then other investigators (Mikati and Saab 2000) have strengthened an immune origin through the evidence of intrathecal IgG index in liquor in patients affected by LKS observing that the rate of IgG was normalized after immunoglobulin treatment. Another evidence of immunological mechanism for epilepsy in LKS was documented by Connolly et al. (Connolly et al. 1999, 2006) through the demonstration of the presence of serum autoantibodies anti-brain endothelial cells and cell nuclei IgG in 45 % of patients affected by LKS in comparison to control. All these observations support the hypothesis that an autoimmune mechanism could be the cause of this epileptic syndrome.

Febrile Infection-Related Epilepsy Syndrome (FIRES)

An expanding interest has been focused on a new important subtype of childhood syndromes called febrile infection related epilepsy syndrome (FIRES).

Just the name of syndrome includes and defines the clinical spectrum of FIRES that is represented by a febrile infection followed, after weeks, by acute onset of an extraordinary high seizure activity most difficult to treat. As first described by van Baalen et al (2010) and Kramer et al. (2011) the population involved in this syndrome is younger than 15 and a slight male predominance. All patients had suffered an infection, mainly respiratory in the weeks prior the onset of symptoms. This syndrome has a poor prognosis and it is burdened by a mortality rate of about 9 % and many patients have cognitive sequelae.

The preceding infection and the lacking evidence of infectious encephalitis support an immune-mediated patho-mechanism for FIRES. Apart from antibody-related encephalitis, alternative hypotheses grant a special role to the innate immune system even to a genetic predisposition in FIRES pathogenesis (Howell et al. 2012; Nabbout et al. 2011)

To date the failure of antibody-detection against the known neuronal antigens as well as the ineffectiveness of immunotherapy questions a role for autoantibodies in the epileptogenesis of classical FIRES (van Baalen et al. 2012).

Despite these limits, the literature data on this syndrome is growing up and an immune involvement is not possible to be excluded. In fact, (Specchio et al. 2010), the presence of severe epileptic syndrome in previously normal children preceded by fever is a highly suggesting element of an immune-mediated or inflammatory processes and it deserves further consideration.

Last Stop: Future Directions

The hypothesis that immune system might have a crucial role in epilepsy was first postulated 20 years ago. Since then, the discoveries in biochemical mediators in epilepsy models plus the possibility to identify an association with specific autoantibodies in several epileptic syndromes are strengthening the relationship between epilepsy and immunity. On the other hand, very interesting is the proven efficacy of immunotherapies such as adrenocorticotropic hormone (ACTH), corticosteroids (dexamethasone, hydrocortisone, prednisone/prednisolone, and methylprednisolone), cyclophosphamide, methotrexate, and rituximab in several forms of refractory epilepsies supporting this link.

Overall, in preclinical settings, the link between inflammation, immune system and epilepsy has to be considered determined, however, more research is warranted in order to better define possible targets for pharmacological interventions and the role played by the various mediators, which is still debated with controversial results being published.

Furthermore some antiepileptic drugs (AEDs) such as valproate, carbamazepine, phenytoin, vigabatrin, levetiracetam, and diazepam have been found to modulate the immune system activity by affecting humoral and cellular immunity (Beghi and Shorvon 2011). Based on these considerations immunity might be considered a promising and enchanting challenge to understand the epilepsy.

Ethical Publication 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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