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REVIEW

Encephalitis and epilepsy

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Abstract Epileptic seizures can be induced by a variety of underlying diseases. One of the causes is brain inflammation or encephalitis. In this review, we focus on three different kinds of encephalitis known to occur with seizures: Rasmussen encephalitis, paraneoplastic encephalitis, and nonparaneoplastic encephalitis. We describe pathogenic similarities and differences in the immunological response and cell death in the central nervous system of these three types of encephalitis and discuss the present ideas regarding the underlying etiology of these diseases.

Keywords Inflammation · Seizures · Encephalitis · Paraneoplastic · Epilepsy

Introduction

Epilepsy is a common brain disorder of cortical origin characterized by recurrent seizures. Seizure disorders are more likely to start in young children or people over the age of 65 years; however, it can occur at any time. Epilepsy is not a single disorder but rather a group of syndromes with a variety of underlying diseases. One of these underlying causes is brain inflammation or encephalitis. Encephalitides can be of infectious or autoimmune origin. Infections are usually due to viruses such as herpes simplex virus; autoimmune processes can be initiated by a (peripheral) neoplasm (see underneath) or by an unknown incent trigger. Three types of such cortical encephalitides often associated with epilepsy have been delineated: Rasmussen encephalitis (RE), paraneoplastic encephalitis (PE), and nonparaneoplastic encephalitis (NPE).

RE is a unihemispheric cerebral inflammatory disorder [1]. Patients suffer from frequent intractable unilateral simple partial focal motor seizures, complex partial seizures, or secondarily generalized seizures. During the disease course, when inflammation spreads across the affected hemisphere, other seizure semiologies indicating newly recruited epileptogenic areas are frequently observed. Within a few months of the manifestation of epilepsy, progressive loss of neurological function associated with one hemisphere starts. After some months and up to 1 year, the main decline is over, and the patient passes into a residual stage with a stable neurological deficit. Due to the atrophy of the affected hemisphere, the neurological functions represented within the affected areas decline continuously. Up until now, hemispherectomy is the only efficient treatment of the pharmacoresistant seizures but inevitably results in irreversible neurological deficits [2–4].

PE refers to symptoms resulting from damage to the central nervous system (CNS) indirectly induced by a remote neoplasm. Many patients with PE have antibodies in their serum that react with both the nervous system and the underlying primary cancer [5]. The presence of these antibodies is diagnostically extremely relevant. Whether these antibodies have a pathogenic role however is still a matter of debate (see below). Paraneoplastic neurological disorders can affect different parts of the nervous system. Some affect only a single area (e.g., limbic encephalitis or brainstem encephalitis) or a single cell type (for instance the Purkinje cells of the cerebellum in paraneoplastic cerebellar

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degeneration (PCD)). In many cases, however, multiple areas of the CNS are involved.

Under the influence of prominent publications [5–8], there has been a tendency to consider encephalitis cases without obvious viral origin in the first line as paraneoplastic in nature. However, an increasing number of reports have shown patients with encephalitis in which extensive diagnostic tests and follow-up failed to reveal an underlying cancer. These cases, which we here group under the name of NPE, have serum antibodies against a variety of neuronal antigens. Such forms of NPE are for example cases with antibodies against NR1–NR2 heteromers of the *N*-methyl-D-aspartic acid (NMDA) receptor, cases with anti-voltage-gated potassium channels (VGKC), and cases with antibodies against glutamic acid decarboxylase (GAD). This type of encephalitis with antibodies against NMDA receptors, GAD, or VGKC can be found associated with and without a tumor [9–11]. The particular antibody is well correlated to distinct neurological syndromes and outcomes. This review describes the pathological mechanisms in these three (RE, PE, and NPE) immune-related disease groups which frequently present recurrent epileptic seizures.

General pathology of immune-related epilepsies

The hallmarks of RE are inflammation, neuronal loss, the presence of microglia activation, microglial nodules, and astrogliosis. These characteristics are present in most cases and have been described in detail [12, 13]. Recently, we expanded the pathology of RE by showing a pronounced loss of astrocytes [14]. The basic pathology of PE [15, 16] and NPE [17–19] does not differ much from RE. There is inflammation in the form of perivascular and parenchymatous lymphocytes, variable neuronal loss, microglia activation with the presence of microglial nodules and astrocyte activation, and gliosis. We investigated the presence of astrocyte loss in PE but, apart from some single apoptotic astrocytes, did not find large astrocyte-depleted areas [14]. Since PE is a conglomerate of encephalitides induced by the presence of different tumors and, like NPE, antibody reactions against various antigens, obviously the localization of neuronal loss and inflammation strongly differs from RE and differs between the different forms. Table 1 lists and compares the predilection sites of RE and the most commonly found forms of PE and NPE.

The inflammatory response

Cytotoxic T cell responses

Analysis of the composition of immune cells in the brains of patients with RE suggests clear evidence that cytotoxic T cells play a role in RE. The T lymphocyte fraction in the brain parenchyma is composed mainly of CD8-positive cells. CD4-positive cells are present but accumulate in the perivascular space of blood vessels rather than migrate into the parenchyma [20]. Other immune cells coming from the bloodstream, like macrophages, B cells, plasma cells, and natural killer cells, are present in low numbers [13, 20]. A dominance of CD8-positive T lymphocytes is not specific for RE but is found in a variety of human CNS inflammatory diseases [16, 21–23]. The inflammation (density of infiltrating T lymphocytes) is inversely correlated with disease duration as well as with neuronal loss; whereas during the course of disease neuronal loss increases, the presence of T lymphocytes gradually subsides to a level which, however, is still well above that found in normal individuals [2]. About 10% of the T cells in the inflammatory lesions are granzyme-B-positive cytotoxic T lymphocytes [20]. Some of these cells were found in close apposition to neurons with polarization

Table 1 Predilection sites of inflammation in RE, PE, and NPE

Encephalitis	Antibody	Syndrome	Predilection site
Rasmussen	(GluR3, Munc-18, Alpha7-ACh receptor)		Frontal, temporal, and parietal cortex
			hippocampus, amygdala (all unilateral)
Paraneoplastic	Anti-Hu	PEM, PCD	Limbic system, brainstem, cerebellum, cerebral cortex
	Anti-Ma-1		Limbic system, brainstem
	Anti-Ma-2	PLE	Limbic system, brainstem
	Anti-Yo	PCD	Purkinje cells in cerebellum
	Anti-NMDAR (NR1/NR2)		Diffuse
	Anti-VGKC		Limbic system
Nonparaneoplastic	Anti-VGKC		Limbic system, basal ganglia
	Anti-NMDAR (NR1/NR2)		Diffuse
	Anti-GAD (GAD 65 kDa)		Cortex, brainstem, spinal cord

of the cytotoxic granules facing the neuronal membrane. This suggests that a cytotoxic T cell response against neurons might be responsible for neuronal loss. Further evidence that a specific T-cell-mediated destruction of neurons occurs in RE comes from studies which show that the local immune response in Rasmussen's syndrome includes restricted T cell populations that expanded from a few, to discrete antigenic epitopes responding, precursor T cells as shown by Li [24] and more detailed recently by Schwab et al. [25].

In PE, studies on a possible role of cytotoxic T lymphocytes are even more fragmented. Since the first description of PE, a number of papers have shown the presence of T cell inflammation in the CNS. In PE with anti-Hu, anti-Yo, or anti-Ma antibodies, a dominance of CD8-positive T cells in the infiltrates was noticed [15, 26–31]. Furthermore, a small number of studies have shown that these T cells contained cytotoxic granules and were in close apposition to neurons [32–34], suggesting that cytotoxic T lymphocytes play a role in neuronal cell death. Although these T cells are found in the neighborhood of neurons, no studies have actually shown the specificity of these cytotoxic T lymphocytes. In addition, no actual evidence has been given that these lymphocytes indeed release cytotoxic substances and thereby are able to kill neurons. Tanaka and colleagues however showed that cytotoxic lymphocytes from a patient with anti-Yo PE could lyse her own Yo protein-expressing fibroblasts [35]. Furthermore, Voltz and colleagues [36] investigated T cell responses and T cell receptor usage in PE with anti-Hu antibodies and showed that an antigen-driven oligoclonal cytotoxic T cell response might play a role in the pathogenesis of anti-Hu-associated PE. A study by Albert from 2000 shows that, in their patients suffering from paraneoplastic cerebellar degeneration, anti-cdr2-specific CD8-positive cytotoxic T cells are present in the cerebrospinal fluid. Treatment with tacrolimus decreases the number of these T cells in CSF but only had a very limited effect on the clinical symptoms [37].

The role of T lymphocytes in NPE is even less clear than in PE. Obviously, since the presence of antibodies against neuronal components such as anti-NMDA receptor (NMDAR), anti-VGKC, and anti-GAD is the key feature of these NPE, not much attention has been given to the role of T cells. Like in PE, some studies show the presence of CD8-positive T cells in the inflammatory infiltrates of patients with anti-NMDAR or anti-VGKC antibodies [18, 19, 38]. Although CD8-positive cells were present in the hippocampus of a case with anti-NMDAR antibodies, staining for cytotoxic granules (TIA-1) showed the absence of these cytotoxic cells in the same area [38]. Figure 1 shows examples of stainings for CD8 and granzyme-B in RE, PE (anti-Ma2), and NPE (anti-GAD).

Antibody-mediated pathogenicity

For a long time, it has been the notion that an antibody-mediated immune response is involved in the pathology of RE. In the 1990s, studies showed that antibodies directed to the glutamate receptor 3 (GluR3) were present in serum of RE patients and were responsible for neuronal damage [39]. Further studies suggested that such antibodies not only killed neurons via an antibody or complement-mediated attack [40] but also that such antibodies might kill neurons via direct activation of the ion channel receptors [41]. As a result of these studies, plasmapheresis in RE patients was started. This treatment indeed seemed to diminish progression of the disease in a number of patients, but improvement was only limited to a short period of time [42], while in a other patients no alleviation of symptoms was found [43, 44]. Later, it became clear that anti-GluR3 antibodies were not present in all RE patients and were not specific for RE but could be found also in other forms of epilepsy [45]. However, since plasmapheresis has a positive effect in some patients, it may be assumed that in a subset of patients indeed autoimmune antibodies with unknown nature contribute to pathogenesis. Potential candidates besides the above-mentioned anti-GluR3 antibodies are antibodies against Munc-18 [46] and the alpha7-acetylcholine receptor [47]. Principal evidence that autoantibodies indeed can cause CNS disease is provided by transfer of anti-GluR1 antibodies into mice brains, which has been shown to induce the symptoms of human GluR1 antibody-associated disease, i.e., ataxia [48].

There is a fair amount of literature on antibodies and their role in PE and NPE. These presentations mostly consist of description of clinical symptoms. The pathological description of the immunopathology of PE and NPE however is scarce and fragmented. Most papers are case reports or descriptions of a few individuals. In addition, pathological workup is rather limited and performed with simple techniques like hematoxylin/eosin or routinely performed immunohistochemistry with CD3 for T lymphocytes and CD68 for macrophages. Moreover, there is a complete lack of quantitative data regarding the presence and the character of inflammatory cells in the CNS.

Despite the fact that for most PE and NPE diseases the presence of neuron-specific antibodies is a known and clinical differentiation factor, there is limited knowledge about the pathological function of these antibodies. In PE with antibodies against intracellular (nuclear) antigens, it is highly doubtful that these antibodies have a pathological function [49]. Transfer experiments to laboratory animals largely failed to reproduce the human disease [50, 51]. Furthermore, there is no correlation between antibody titers and the disease severity [52]. In addition, an early study from Verschuuren in a case of PE with anti-Yo antibodies

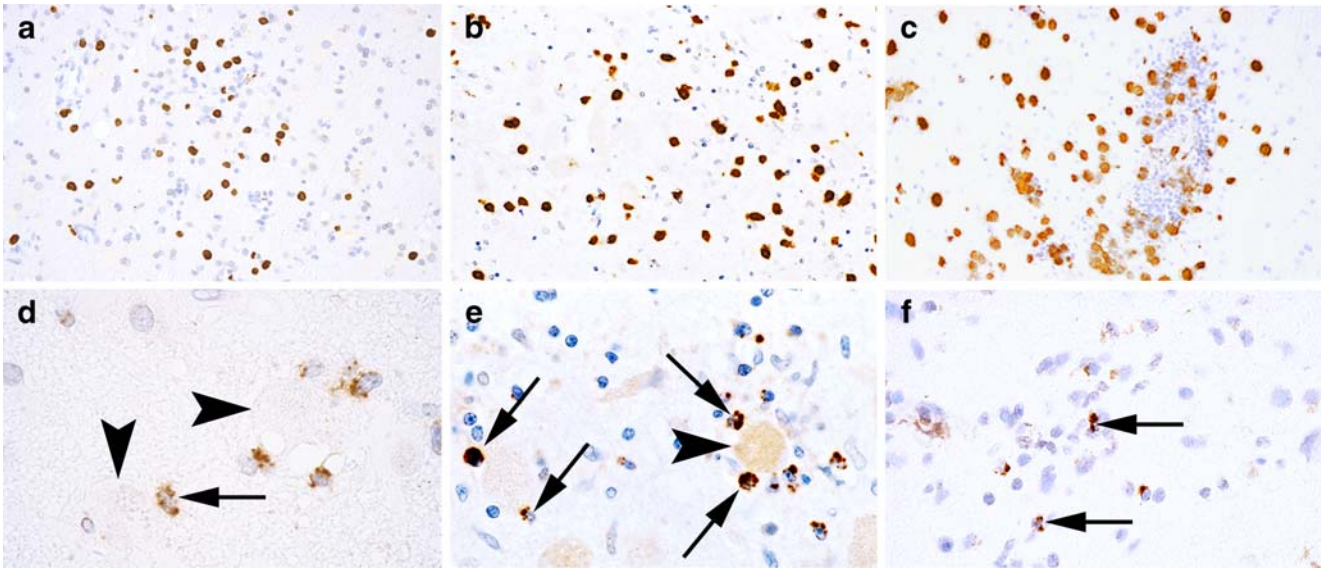

Fig. 1 Stainings for CD8-positive and granzyme-B-positive cytotoxic T lymphocytes and hematoxylin counterstain for nuclei in RE (**a** and **d**), PE (**b** and **e**), and NPE (**c** and **f**). **a**, **b**, and **c** show infiltration of numerous CD8-positive cytotoxic T lymphocytes in RE (**a**), a PE case with anti-Ma2 antibodies (**b**), and an NPE case with anti-GAD antibodies (**c**). **c** shows a perivascular cuff with many CD8-positive cells but also nuclei of unstained cells. Most of these unstained cells are CD4-positive lymphocytes which remain in the perivascular space of the blood vessel. **d**, **e**, and **f** show stainings for granzyme-B. In RE (**d**) and the anti-Ma2 PE case (**e**), multiple cytotoxic T cells (*arrows*) can be found close to two neurons (*arrowheads*). The NPE (anti-GAD) case shows some GrB-positive lymphocytes in the parenchyma, which are not associated with neurons

showed the absence of large quantities of anti-Yo in the CNS [30]. Specific staining for anti-Hu, anti-Ma1, or anti-Ma2 in the respective encephalitis brains should look similar to staining of sera of anti-Hu and anti-Ma patients on rat or human brain [53] and thus should predominantly be found in a nuclear localization. Staining for immunoglobulins (Ig) in anti-VGKC or anti-NMDA receptor encephalitis brains should correspond to stainings done with sera from these cases on rat brain and thus should be present in a dendritic localization on the membranes of cells. In the study of Verschuuren, a negative result for anti-Yo antibodies in the CNS was shown. Unfortunately, the opposite, a positive immunohistochemical staining for Ig in the CNS, is often incorrectly used as evidence for a pathological function of antibodies. For example, staining in the CNS of PE with antibodies against anti-Hu or anti-Ma2 show cytoplasmic staining in neurons [34] where one, in addition, should see a dominant staining of the nucleus. Similar results are found in NPE cases with antibodies against membranous determinants such as anti-VGKC or anti-NMDA receptor in which cytoplasmic staining of neurons, instead of membranous deposition, is presented as evidence for a pathogenic role of anti-NMDA receptor antibodies [19]. For GAD65 antibodies in NPE, the situation is more complex. GAD65 is located in the membranes of gamma-aminobutyric acid (GABA)-containing vesicles and as such is considered an intracellular antigen. However, during exocytosis of GABA, GAD65, which is located on the interior surface of the vesicles, will be exposed on the cell surface because the vesicles turn inside out as they fuse with the plasma membrane [54, 55]. Therefore, GAD65, although predominantly found inside of neurons, in addition, should be considered a membranous antigen. The examples above show that interpretation of Ig distribution and deposition in human brain samples is difficult and thus should be interpreted with caution. Most of the time, Ig stainings are performed on paraffin material in which, due to blood brain barrier leakage, due to post mortal changes in autopsy specimens, or in biopsy specimens, due to manipulation-related pressure on the tissue, there is a large amount of Ig diffused in the CNS parenchyma. Neurons and glial cells damaged during the disease process or under specimen sampling conditions can take up these Igs, leading to a pattern of cytoplasmic staining of these cells which often is interpreted as "disease specific." A recent paper by Barnett et al. warns against this technical problem of aspecific staining which also is found in other neurological diseases [56].

The basic question for PE and NPE is whether autoantibodies against nuclear or intracellular antigens can penetrate into living undamaged cells in vivo. In systemic lupus erythematosus research, this question has been asked for over 20 years and still has not been answered unequivocally [57]. Supporters of the concept of penetration of antibodies in living cells promote the finding of penetration of

antibodies in cultured cells [58]. However, to date, only one single paper from 1999 describes the penetration of autoantibodies into living cells in vivo [59]. It has been shown that transfer of human antibodies against surface antigens (GluR1) in mice can elicit neurological symptoms [48, 60]. At present, there are however no studies which prove that transfer of antinuclear or anticytoplasmic antibodies can do the same.

Overall, the present view is that (paraneoplastic) encephalitis with its antibodies to intracellular antigens and encephalitis (both nonparaneoplastic as well as neoplastic) with antibodies to neural surface antigens reflect different pathogenic mechanisms. Whereas the encephalitides with nuclear/intracellular antibodies are mediated by cytotoxic T cells, the encephalitides with antibodies to neural surface antigens may well be mediated by pathogenic antibodies [49]. One argument in favor of this hypothesis is that PE responds poorly to removal of antibodies whereas patients with VGKC or NMDAR antibodies often seem to respond positively to plasmapheresis [10, 61, 62].

Neuronal death in these epilepsies

Loss of neurons is a common feature of RE, all PE, and all NPE. In RE, loss of these neurons generally is found in cortical areas [12]. In PE, neuronal loss depends on the localization of proteins for the specific antibodies. For instance, PCD with anti-Yo antibodies leads to a strict loss of Purkinje cells in the cerebellum [30], while in PE with anti-Ma2 antibodies neuronal degeneration predominantly is found in brainstem or the limbic system [63]. Although, in all these different forms of PE, neuronal loss is obvious, there is very little information on how and when these neurons actually die. Basically, these cells can die by either apoptosis or necrosis. In case of neuronal cell death due to a cytotoxic T cell response, apoptosis is the main form of cell death. After attachment to their target cells, cytotoxic T lymphocytes can kill their targets by release of granzyme-B which induces apoptosis by caspase-dependent mechanisms [64]. In PE with Ma-2-specific antibodies, cytotoxic T lymphocytes have been shown in close apposition to neurons. In the same study, the authors however found no evidence of neuronal apoptosis. [16]. When the absence of apoptosis was not the result of a too insensitive system, this means either that, although these T lymphocytes are in near vicinity of neurons, actual release of granzymes does not occur or that cell death is mediated by non-caspase-dependent mechanisms. The most likely possibility however is that the majority of acute neuronal death only occurs during the early stage of the disease and is no longer detectable at the time of autopsy, i.e., some time after disease onset. In NPE or PE with antibodies against nuclear or membranous neuronal antigens, neurons also might die by an antibody-mediated mechanism [49]. However, neuronal damage, especially in NPE with membranous antibodies, is relatively little [38, 65, 66], and acute death of neurons by terminal deoxynucleotidyl transferase dUTP nick end labeling reactivity has not been shown yet. Problem with NPE brain is that these diseases of ten have a much milder disease progression and longer disease duration, and therefore neuronal cell death may not be actively present at the time of autopsy [38]. In addition, patients with surface antigen antibodies have a more favorable outcome of therapy [67], and thus pathological investigation of these brains is rather rare.

Concluding remarks; a relationship between inflammation and seizures?

A question which has not been dealt with is the relationship between inflammation in the CNS and the epileptic seizures. Animal models of epilepsy have provided evidence that experimentally provoked seizures trigger an inflammatory response in the CNS. During this response, a large range of inflammatory substances such as IL-1β and TNF-α are produced. These mediators, produced by microglia/macrophages, i.e., cells of the innate immune system, can induce and/or enhance epileptic seizures [68–70]. So far, in these experimental models, there is no support that the seizure activity itself induces a prominent secondary recruitment of cellular elements of the adaptive immune system (B and T lymphocytes) [70]. In human disease, a direct relationship between inflammation and seizures remains unclear and is difficult to study. The interactions between innate and adaptive immune system, with its complex of immunomediatory and neuroregulatory mediators on the one hand and excitatory neurons on the other hand, certainly are extremely different in the various forms of epilepsy. There are however some points which we have learned from RE. First, it has been shown that inflammation can precede the occurrence of seizures rather than the opposite in which seizures induce inflammation with influx of lymphocytic cells [71, 72]. In addition, magnetic resonance imaging (MRI) studies indicate that inflammatory disease activity in RE may occur outside of the epileptic network, suggesting that inflammation in RE is at least partially independent of epileptic activity [73]. Further evidence arguing against a direct effect of inflammation on seizure induction comes from therapeutic studies with tacrolimus. In RE patients, tacrolimus had a positive effect on conservative of motor and cognitive functions and on brain tissue, but had no effect on seizure frequency [74]. The role of antibodies on the induction of seizures is another thing which is still largely unclear. Plasmapheresis in RE,

VGKC, or NMDAR encephalitis can provide a positive effect on the number of seizures or on other neurological symptoms [10, 42, 61, 75]. Furthermore, in NMDAR encephalitis, recovery of neurological signs is related with a decrease of serum antibody titers. In addition, in these patients, MRI shows normalization or improvement of brain areas after intravenous immunoglobulin therapy or plasmapheresis, indicating that damage was reversible. Finally, the few cases which were biopsied revealed no evidence of neuronophagia [10]. This and the finding that antibodies from the NMDAR encephalitis patients cause a reversible decrease in number of postsynaptic clusters of NMDAR [10] all point in the direction that in these NMDAR encephalitis cases neurological damage is not mediated by a real antibody-mediated induced death of neurons but rather by a physiological effect of binding of these antibodies to NMDA receptors.

In conclusion, epileptic disorders such as RE, PE, and NPE show inflammatory reactions in the CNS. Pathological damage to the brain and induction of seizures can be achieved by inflammatory mediators from the innate immune system, something which is clearly shown in animal models of epilepsy but is largely undiscovered in human epilepsy. In addition, the adaptive immune system in the form of cytotoxic T lymphocytes or pathogenic antibodies against intracellular or membranous antigens may play a specific role in the pathogenesis. The antibodies are important diagnostic markers. In addition, those against membranous antigens seem to have a pathogenic effect. To what extent the paraneoplastic antibodies against intracellular antigens play a role still needs to be clarified.

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