

## Autoimmune epilepsies in children

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### ABSTRACT

The role of the immune system in epilepsy is illustrated by pathological changes consistent with inflammation in surgical specimens excised from refractory epilepsy patients, various inflammatory mediators measured in the central nervous system of epilepsy patients, and recently by the discovery of new neuron-specific antibodies against plasma membrane proteins in encephalopathies and epilepsy. Both the innate immune system, consisting of cytokines and toll-like receptors, and adaptive immune system, in collaboration with anti-neuronal antibodies, are involved in neuroinflammation. Epidemiological studies indicating a close relationship between epilepsy and other systemic autoimmune disorders, and clinical response to immunomodulatory agents provide additional support for the involvement of inflammatory pathogenesis in epilepsy. Nevertheless, new studies are needed to establish the autoimmune and inflammatory theory as well as to define the clinical spectrum of autoimmune epilepsy.

**KEYWORDS:** epilepsy, immunity, inflammation, children

### INTRODUCTION

Expanding knowledge on the mechanisms of inflammation and the identification of serum markers have enabled the identification of possible causes in many disorders of previously unidentified etiology including epilepsy which is one of the

most frequently diagnosed disorders in neurology [1]. Almost any congenital, genetic, or developmental event that causes structural or functional disturbance in the brain can lead to epilepsy. However the underlying cause is still unknown in many epileptic disorders. A role for inflammatory and/or autoimmune mechanisms, either independently or in combination with other factors, appears possible. Seizures as part of the symptomatology in systemic autoimmune diseases such as systemic lupus erythematosus or Hashimoto thyroiditis, the presence of antibodies in the serum and cerebrospinal fluid of epilepsy patients, inflammatory lesions on their MRI, and response to immunosuppressive treatment in certain epilepsy cases support this hypothesis [2-4].

Immunologic reactions in the brain involve both the innate immune system, consisting of cytokines and toll-like receptors, and the acquired immune system, particularly through anti-neuronal antibodies. [1, 5-7]. Glial cells are direct players of these processes: when seizures occur, members of the TLR family are significantly upregulated in the microglia together with an increase in cytokines and chemokines. These in turn contribute to seizure-related hippocampal pathology and neuronal death [8].

### Autoantibody-related epilepsies

Autoimmune processes in seizures were first identified in acute limbic encephalitis caused by anti-neuronal antibodies, followed by the discovery of antibodies in many cases of encephalitis complicated by seizures. Although the terms antibody-mediated encephalitis and antibody-mediated

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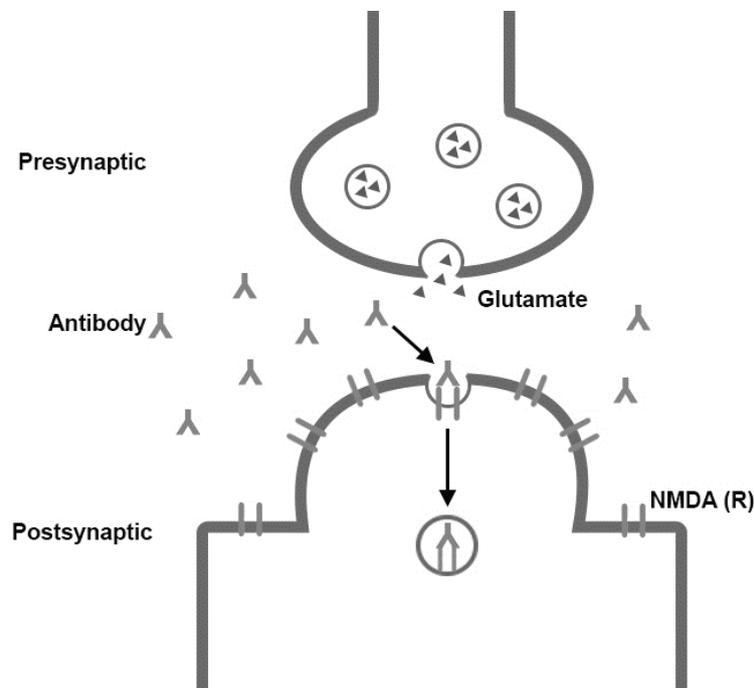
epilepsy are frequently used interchangeably in the literature, not all autoimmune epilepsies are the result of autoimmune encephalitis. There is the possibility of autoantibody-related epilepsy in patients with a subacute onset of seizures especially in the presence of a personal or family history of autoimmune disorder or a personal history of tumor [2]. Rapid identification is extremely important because early immunomodulatory treatment allows full recovery [9]. There is little doubt that many more antibodies remain to be identified and therefore the absence of seropositivity does not rule out autoimmune epilepsy.

The potential role of autoantibodies in epilepsy pathogenesis has been attracting interest in recent years. The first anti-neuronal antibodies Anti-Hu, Ma-1 and Ma-2, CRMP-5 and amphiphysin were detected in patients with a neoplasm. Therefore thorough investigation in such cases for tumors of ovaries, testes, lung, breast or lymphoid system was recommended [2, 10]. Subsequently, autoantibodies against the following antigens were identified in the absence of tumors especially in childhood epilepsy and encephalopathies: voltage-gated potassium channels (VGKC) whose antigenic

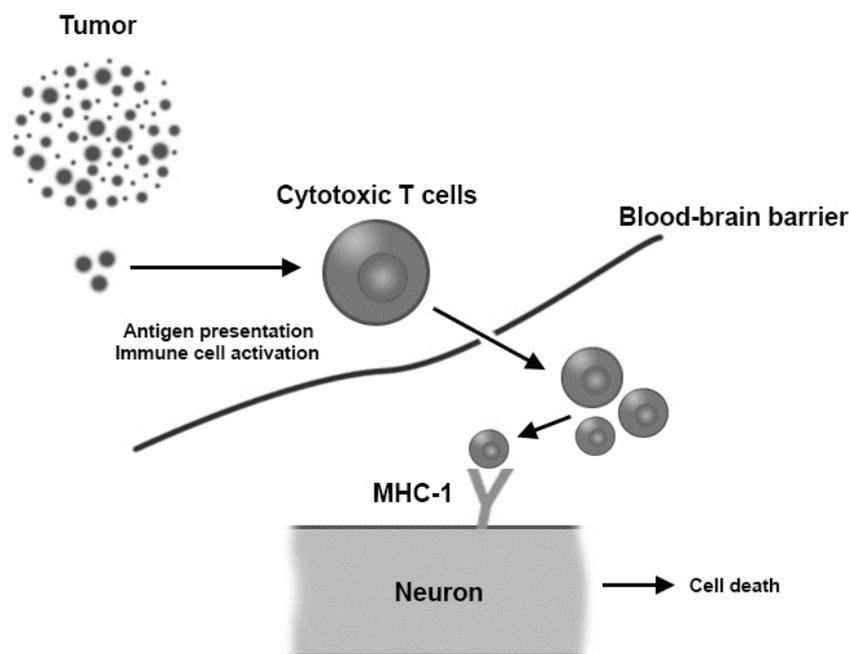
components are leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein 2 (CASPR2) in adults but not in children, glutamic acid decarboxylase (GAD), N-methyl-D-aspartate receptor (NMDAR),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), gamma-amino butyric acid-B and -A receptors (GABA<sub>B</sub>R and GABA<sub>A</sub>R) and glycine receptors. All of them except GAD are neuronal membrane surface proteins [11]. Ongoing studies support the hypothesis that when antibodies are formed against intracellular antigens like GAD, neurodegeneration is mediated by T cells, whereas if antibodies are against a surface antigen like GABA<sub>B</sub>R, they are directly responsible for the neurological impairment [12]. The pathogenesis involves internalization of antibody-bound NMDARs and perhaps LGI1 receptors rather than immunedestruction (Fig. 1 and Fig. 2) [13, 14].

#### Chronic focal inflammation: Rasmussen's encephalitis (RE)

This particular form of epilepsy with drug-resistant focal seizures, progressive hemiplegia, cognitive deterioration, and atrophy of one cerebral



**Fig. 1.** Immune pathogenesis of NMDAR encephalitis.



**Fig. 2.** Immunopathogenic mechanism of paraneoplastic syndrome.

hemisphere is a focal, chronic inflammation. The possible pathogenic mechanisms include T-cell cytotoxicity and antibody- and microglia-mediated degeneration. The first antibodies identified in RE were against the glutamate receptor GluR3; however this finding has been reproduced in only a fraction of patients. Therefore the role of central nervous system (CNS) autoantibodies in the pathogenesis of RE is still unclear [15-17]. Cytotoxic T lymphocytes sensitized against one or more neuronal antigens stimulate the local synthesis of interleukin-1  $\beta$  and other inflammatory mediators, and with potential contribution of autoantibodies, cause astrogliosis and neuronal death [1, 18-20]. Anti-epileptic medications fail to provide seizure control in most cases, and hence hemispherectomy is recommended. Treatment with T cell-inactivating drugs such as corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, tacrolimus and azathioprine show some effect, supporting the role of immune mechanisms in the pathogenesis of RE [15].

### **Fever-associated seizures**

The immune system, and particularly innate immunity, takes part in the pathogenesis of benign childhood febrile seizures seen in about 2-5% of

children younger than 5 years [21]. Proinflammatory cytokines and chemokines released during fever may activate ion channels, triggering neuronal hyperexcitability and seizure formation [22]. Interleukin-1  $\beta$  (IL-1 $\beta$ ) was shown to be increased in the serum of patients with febrile seizures [21]. A positive family history is often found in children with febrile seizures and the genetic link may include single-nucleotide polymorphisms (-174, -572 and -597) in the IL-6 gene, which are higher in patients compared to controls [21-23].

Serious conditions associated with fever and epilepsy are the febrile infection-related epilepsy syndrome (FIRES) and the idiopathic hemiplegia-hemiconvulsion syndrome (IHHS). Both disorders are rare syndromes characterized by the occurrence of status epilepticus in a previously healthy child during or closely after a febrile episode. The triggering by fever suggests a role for the inflammatory cascade. FIRES was first identified in 1986. It follows a simple febrile disorder, usually acute respiratory infection, manifests with focal seizures and refractory status epilepticus, and results in drug-resistant epilepsy and neuropsychological impairment [24]. Genetic and autoimmune mechanisms are considered in the etiology in some subjects, but although the presence

**Table 1.** Key features of inflammatory and antibody-related epilepsies.

| Disorder                                      | Related immune mechanism     | Target (Ag)  | Other evidence  | Reference   |
|---|------------------------------|--|---|-------------|
| Rasmussen's encephalitis                      | CD8+ lymphocytes<br>Antibody | Microglia and astroglia<br>Glutamate receptor 3                                  | Oligoclonal bands   | [1, 19, 37] |
| Febrile infection-related epilepsy syndrome   | Unknown                      | Unknown  | Infection (suspected)   | [19]        |
| Idiopathic hemiplegia-hemiconvulsion syndrome | Unknown                      | Unknown  | Infection (suspected)   | [19]        |
| Antibody-mediated epilepsies                  | Antibody                     | VGKC complex (leucine-rich glioma-inactivated 1, contactin-associated protein 2) | Oligoclonal bands   | [1, 37]     |
|   | Antibody                     | Gamma-amino butyric acid-B   |   |             |
|   | Antibody                     | N-methyl-D-aspartate   | Oligoclonal bands, lymphocytic pleocytosis and elevated protein | [2, 37]     |
|   | CD8+ lymphocytes<br>Antibody | Neurons<br>Glutamic acid decarboxylase   |   | [10]        |

of anti-VGKC, anti-GAD and anti-GluR3 antibodies as well as response to immunotherapy have been observed in a few patients, the evidence for autoimmune pathogenesis is unclear. No inflammatory infiltration was observed in the brain biopsy of children with FIRES. IHHS is characterized by unilateral and usually clonic epilepsy that emerges during a febrile disorder and is followed by temporary or permanent ipsilateral hemiplegia [25-30].

The etiopathogenesis of FIRES and IHHS is being investigated in experimental models mimicking these two conditions. Nabbout *et al.* in their review of inflammation-mediated status epilepticus, emphasize the role of IL-1 $\beta$  and tumour necrosis factor (TNF) in increasing excitability through

increasing glutamate in the extracellular micro-environment, and altering ion channel functions and calcium permeability and hence predisposing to seizures [31]. These findings do not prove the role of inflammatory mechanisms in the neurological picture, but support their contribution in the persistence of seizures.

#### **Treatment in immune-mediated epilepsy syndromes**

A response rate of 60-80% is reported for immune treatment in adults with autoimmune encephalitis, but information in children is limited [22]. First-line treatment includes corticosteroids, IVIG, and plasma exchange in the acute stage [32]. In children, high doses of IV methylprednisolone or

IVIG are first administered [2]. The European Federation of Neurological Societies recommends IVIG treatment in pediatric refractory epilepsies [33]. The response rate of IVIG therapy has been reported to be around 30-50% [34]. Plasma exchange is also a useful acute treatment method and is commonly used in critically ill patients or patients who cannot tolerate intravenous steroids or IVIG. If there is no response to these first-line drugs, azathioprine, cyclophosphamide, the anti-pre-B-lymphocyte monoclonal antibody rituximab, monoclonal antibodies such as efalizumab or natalizumab, and agents such as mycophenolate are tried [2, 11, 35]. While the prognosis is poor in those who have antibodies against intracellular onconeural antigens, the response to immune treatment is better in those who have antibodies against surface proteins [2, 36]. Certain patients enter spontaneous remission; on the other hand, some others may have to receive lifelong immunosuppressant treatment [2]. Treating physicians should distinguish the sequelae of the initial episode from an ongoing immune process: the absence of remission does not necessarily imply that the inflammatory reaction is still active. Long-term immunotherapy is to be administered in case of progression in neuroimaging findings, persistence of inflammatory markers in the CSF, or recurrence of the symptoms when acute treatment is discontinued.

## CONCLUSION

Although target antigens or related mechanisms of all inflammatory and antibody-related epilepsies are not known exactly (Table 1), an inflammatory mechanism should be suspected in all epilepsy cases refractory to treatment and in patients with unexplained, subacute onset of seizures who have inflammatory findings in the cerebrospinal fluid or on MRI. If Koch's postulates described for microbiology were to be applied to autoimmunity, induction of the disease by passive transfer of autoantibodies and/or autoreactive T cells to susceptible animals would provide definitive proof for the pathogenesis. Although this has not been demonstrated in all the clinical conditions summarized above, the possible favorable response to high-dose steroids and/or IVIG supports early administration of immunomodulatory treatment.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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