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Review

Immunological aspects of epilepsy

Radosław Zarczuk[1], Dariusz Łukasik[1], Marian Jędrych[2], Kinga K. Borowicz[1]

[1]Experimental Neuropathophysiology Unit, Department of Pathophysiology, Medical University, Jaczewskiego 8, PL 20-090 Lublin, Poland

[2]Department of Biostatistics, Medical University, Jaczewskiego 4, PL 20-090 Lublin, Poland

Correspondence: Kinga K. Borowicz, e-mail: kinga.borowicz@am.lublin.pl

Abstract:
In recent years, the concept of an immunological background of some types of epilepsy has been gaining an increasing number of supporters. The following article is an attempt to review the most significant studies that explore irregularities in patients with intractable epilepsy, search for and identify the immunological causal factors of seizures and, finally, associate these factors with particular syndromes that manifest in refractory epilepsy. We also discuss the efficacy of immunomodulatory treatment in the recognized syndromes. Last, we focus on the immunological abnormalities found in patients undergoing antiepileptic therapy with classical antiepileptic drugs as well as changes in the immune system that could be provoked by an epileptic seizure itself.

Key words:
epilepsy, immunology, *Rasmussen encephalitis*, systemic lupus erythematosus

Abbreviations: ACL – anticardiolipin antibodies, ACTH – corticotrophin, AED – antiepileptic drugs, AMPA – α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, ANA – antinuclear antibodies, APL – antiphospholipid antibodies, APS – antiphospholipid syndrome, CBZ – carbamazepine, CNS – central nervous system, CRH – corticotropin-releasing hormone, CSF – cerebrospinal fluid, EEG – electroencephalogram, EPSPs – excitatory postsynaptic potentials, FGF – fibroblast growth factor, GA – glutaric acid, GABA – γ-aminobutyric acid, GAD – glutamic acid decarboxylase, GluR3 – glutamate receptor type 3, GluR3Ab – antibodies against glutamate receptor type 3, IL – interleukin, IL-1Ra – IL-1 receptor agonist, IFN – interferon, IPSPs – inhibitory postsynaptic potentials, IVIG – intravenous immunoglobulins, LA – lupus anticoagulant, LGS – Lennox-Gastaut syndrome, LKS – Landau-Kleffner syndrome, MAC – membrane attack complex, MCP-1 – monocyte chemoattractant protein-1, MMA – methylmalonic acid, NK – natural killer, NMDA – N-methyl-D-aspartic acid, PB – phenobarbital, PHT – phenytoin, PMN – polymorphonuclear leukocytes, PTZ – pentylenetetrazole, RE – *Rasmussen encephalitis*, SE – status epilepticus, SLE – systemic lupus erythematosus, TNF-α – tumor necrosis factor-α, VGCC – voltage-gated calcium channels, VGKC – voltage-gated potassium channels, VPA – valproic acid, WHO – World Health Organization, WS – West syndrome

Introduction

Epilepsy is a chronic disorder characterized by recurrent unprovoked seizures of cerebral origin with motor, sensory or autonomic disturbance with or without loss of consciousness [90]. According to estimates from the WHO, the mean prevalence of active epilepsy is approximately 8.2 per 1000 people in the general population, which renders it likely that as many as 50 million people throughout the world may be af-

fected with this disease. However, as observations made over the years have proven, epilepsy is not a homogeneous disorder, but a group of pathologic conditions that manifest with seizures. Although the seizure pattern may look similar or even identical in people with epilepsy, the underlying pathology may differ. Regarding its etiology, epilepsy has been divided into types: idiopathic generalized (genetic), symptomatic (with known cerebral abnormality) and cryptogenic (with the causative factor still to be identified) [90].

Intense research into the mechanisms of epilepsy and the function of the central nervous system (CNS) has led to the formulation of a theory that suggests that seizures are caused by an imbalance between the excitatory and inhibitory stimuli that interact with a group of neurons of a particular epileptic focus. When the excitatory postsynaptic potentials (EPSPs) gain advantage over the inhibitory postsynaptic potentials (IPSPs), an abnormally high depolarization may be generated, thus triggering a series of action potentials. The processes known to play a role in neuronal depolarization are calcium and sodium influx, potassium efflux, excitation *via* amino acids (e.g., glutamate) and inhibition *via* neurotransmitters (i.e., GABA) [83]. It is on the aforementioned mechanisms that the contemporary therapy of epilepsy is based. Yet a group still exists of approximately 20–40% of patients who are drug-resistant [37].

The considerable prevalence of drug-resistance and the large number of cases that fall into the cryptogenic group of epilepsies implies that there must be other mechanisms responsible for the development of certain types of epilepsy that remain undiscovered. This theory led to a growing interest in the possibility that autoimmune mechanisms play a role in epileptogenesis and resulted in a large number of reports on the subject. These reports describe the presence of autoantibodies and other immunological alterations in patients with epilepsy as well as evidence of the epileptogenic properties of those antibodies and the positive effects of immunomodulatory treatment of certain types of epilepsy.

In the beginning, most studies searching for any association between the immune system and epilepsy were performed on unselected groups of epileptic patients. Those works compared the serum levels of non-specific immunoglobulins, especially IgG and IgA. In 1988, Eeg-Olofson et al. [30] reported significantly decreased mean serum levels of IgA in patients with focal epilepsy compared with a control group, while their relatives displayed considerably decreased mean levels of IgM. However, it was argued whether these immunoglobulins constitute a contributory factor or if their presence is simply a result of seizure activity.

Other experiments using antibodies directed against the forebrain or hippocampus provided evidence that their intracerebral application might induce seizures in animals [79].

Anti-GluR3 antibodies (*Rasmussen encephalitis*)

The first specific immunologic factors suspected of contributing to the development of epilepsy are the antibodies against glutamate receptor type 3 (GluR3). Glutamate receptors, also referred to as AMPA, are non-NMDA-type ionotropic transmembrane postsynaptic receptors. They are composed of four types of subunits, GluR1-4, which combine to form tetramers. These structures are responsible for fast synaptic transmission and are common in the CNS. The role of the GluR3 subunit of the AMPA receptor in epilepsy was examined by Steenland et al. [101], who demonstrated that three out of nine genetic knockout mice, GluR3 (–/–), expressed spontaneous seizure activity. In 1994, Rogers et al. [92] found anti-GluR3 antibodies in the serum of patients suffering from *Rasmussen encephalitis* (RE).

RE is a rare progressive neurodegenerative syndrome characterized by intractable focal seizures, cognitive decline and hemiparesis. The disease usually has its onset in childhood, and the neurodegenerative process affects only one cerebral hemisphere, causing a typical image of encephalitis with perivascular lymphocyte cuffs and scattered microglial nodules. These changes progress and lead to neuronal and cortical cell loss [13].

In his experiments, Rogers et al. [92] also proved that immunization of rabbits with GluR3 induced seizures. Moreover, the histopathological picture of these rabbits mimics that found in patients with RE. The crucial difference is that in the experimentally induced disease, the pathology involves both hemispheres, whereas in patients with RE, the changes are unilateral. The unilateral involvement of the brain in this disease is, however, contradicted by Andermann and Farrell [4] who, after analysis of the available