Review

PREVALENCE OF ANTICARDIOLIPIN, ANTI-BETA2-GLICOPROTEIN-I AND ANTINUCLEAR ANTIBODIES IN CHILDREN WITH EPILEPSY

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Summary

Epilepsy is characterized by the occurrence of chronic seizures without any provocation. The cause of epilepsy is often multifactorial. In "cryptogenic epilepsy", for example, no cause can be identified in approximately 30% of the cases. A high prevalence of epilepsies in specific immunological diseases suggests that the immune system may play a role in the pathogenesis of epilepsy or might be associated with it. Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. With the advance in immunology, many studies have been conducted to clarify the role of the immune system in the pathogenesis of epilepsy. It has been proved that most of the children with idiopathic form of epilepsy without clinical or serological markers of connective tissue disease have elevated titers of various autoantibodies which cause immune-mediated neuronal damage. The role of immune mechanisms in epilepsy suggests the need for clarification and compliance with the immunological status regarding the presence of antinuclear, antiphospholipid, anti-beta2-glicoprotein-I and other autoantibodies in the course of treatment, and an opportunity to apply immunomodulating therapy for better control on the incidence and severity of attacks.

Key words: epilepsy, autoantibodies, children

Introduction

Epilepsy in children is considered as one of the most prevalent neurological condition, characterized by the occurrence of chronic seizures without any provocation. These seizures take place due to excessive and abnormal activities in a child's brain. Worldwide, it is estimated that 10.5 million children under 15 years of age have active epilepsy, representing about 25% of the global epilepsy population [1]. Childhood-onset epilepsy indicates annual incidence rate of 40 to 70 per 100 000 and 2 to 4 times higher mortality [2]. The cause of epilepsy is often multifactorial. In many cases, epilepsy is the result of a complex interaction of genetic and environmental factors. Most diseases affecting the cerebral grey matter can result in epilepsy. Approximately 10% to 30% of all epilepsies are likely to have a predominantly genetic cause,

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although many genes are probably involved. In a small number of cases, a single genetic cause can be identified. Congenital causes account for approximately 10% of cases. The commonest acquired causes of epilepsy are vascular, tumour-related, post-traumatic, or post-infectious. In approximately 30% of the cases, no cause can be identified - these cases are referred to as 'cryptogenic epilepsy'.

A high prevalence of epilepsies in specific immunological diseases suggests that the immune system may play a role in the pathogenesis of epilepsy or might be associated with it. Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. Autoantibodies are present in low titers in the general population, but in about 5% of the population, their concentration is increased.

Immunological aspects of epilepsy

Antinuclear antibodies (ANAs) are found in patients whose immune system may be predisposed to cause inflammation against their own body tissues. ANAs indicate possible presence of autoimmunity and possibility of autoimmune illness.

Hughes syndrome (the antiphospholipid syndrome) presents with recurrent thrombosis, recurrent miscarriage and neurological disease. The major pathogenic mechanism of the syndrome is vascular obstruction (both venous and arterial) due to hypercoagulability. The brain is the organ most dramatically affected in Hughes syndrome. Neurological manifestations are prominent, and are often the dominant feature. Headache, migraine, cognitive dysfunction, epilepsy, chorea, multiple sclerosis (MS), psychiatric disease, transverse myelitis, ocular syndromes, sensorineural hearing loss and movement disorders are common [3].

The role of autoantibodies, mediating inflammation in epilepsy has been of increasing interest since the first description of anti-GluR3 antibodies in Rasmussen encephalitis. In subsequent studies, these antibodies were also described in some other severe localization-related epilepsies. Autoantibodies have been also implicated in refractory epilepsy but their pathogenetic significance is less well established. An increased prevalence of antiphospholipid antibodies was demonstrated among patients with epilepsy without any connective tissue disease.

Antibodies of another class with possible etiologic significance are those against GM1 gangliosides, which are a component of synaptic membrane and a major regulator of ion currents. GM1 antibodies have shown to be epileptogenic in experimental studies. They have been measured in patients with therapy resistant, localization-related epilepsy. Antibodies to glutamic acid decarboxilase (GAD), the enzyme that catalyzes the conversion of L-glutamic acid to GABA, were found in patients with refractory focal epilepsy. Immunoglobulin A (IgA) deficiency has been detected in up to 25% of patients with epilepsy. Imbalance of other immunoglobulin subclasses also occurs [4]. A high prevalence of epilepsy in specific immunological diseases (e.g. 1-5% in celiac disease, 10% in systemic lupus erythematosus) suggests that aberrations of the immunological system may be associated with epilepsy.

With the advance in immunology aspect, many studies were conducted to clarify the role of the immune system in the pathogenesis of epilepsy. In a cross-sectional study carried out by Ranua et al., the presence of autoantibodies was determined in a representative cohort of 960 patients with epilepsy [5]. The frequency of antinuclear antibodies (ANA), immunoglobulin G class anticardiolipin antibodies (aCL) and anti-beta2-glycoprotein I antibodies were studied in 960 patients with epilepsy and in 580 population-based reference subjects identified from the Finnish Population Registry. Patients with partial epilepsy and more than one seizure per month were 2.2 times more likely to have aCL than patients with partial epilepsy with less than one seizure per month.

It is well known that aCL antibodies significantly increase the risk of both venous and arterial thrombosis [6, 7]. For patients with aCL antibodies, no spontaneous thrombotic events were noted in the past history, nor were there other clinical features of antiphospholipid antibody syndrome. The aCL antibodies could also reflect a common, perhaps genetically determined, predisposition to develop epilepsy and to produce autoantibodies [8]. Two pathogenic mechanisms have been proposed to explain the relationship between aCL antibodies positivity and epilepsy thrombotic and ischemic events within the CNS [9, 10] and an autoimmune reaction to antigens expressed specifically by neurons that have an epileptic activity [15, 16]. Moreover, ANA tended to be more frequent among patients with more than one seizure per

month. No association was found between the major antiepileptic drugs and autoantibodies. However, a long duration of epilepsy and poor seizure control were associated with an increased presence of aCL in patients with partial epilepsy [5].

A study performed by Verrotti et al. proved the hypothesis that raised anticardiolipin antibodies, glutamic acid decarboxylase (GAD) and antinuclear antibodies were associated with epilepsy and/or pharmacoresistance. Titers in 74 epileptic patients and 50 controls were studied [11]. Epileptic patients were divided into two groups according to their response to anticonvulsant therapy. Group I included 52 children (30 females and 22 males with a mean age±SD of 7.0±2.4 years) suffering from different types of epilepsy and treated with various anticonvulsants. Group II included 22 children (10 females and 12 males with a mean age of 6.2±3.6 years) suffering from therapy-resistant epilepsy. It was found that the prevalence of anticardiolipin antibodies was significantly higher in epileptic patients than in controls, while there was no significant difference between patients who were seizure-free and those with uncontrolled epilepsy. No significant difference was found in glutamic acid decarboxylase antibodies between epileptic children and controls, and between patients who were seizure-free and those with uncontrolled epilepsy. A significant difference in the incidence of antinuclear antibodies was found between the epileptic children and the controls, while no difference was found between well-controlled and drug-resistant epilepsy. In conclusion, the prevalence of anticardiolipin and antinuclear antibodies was higher in patients with epilepsy than in controls. There was no significant difference in serum glutamic acid decarboxylase antibodies between the epileptic children and controls, and between patients who were seizure-free and those with uncontrolled epilepsy (Table 1 and Table 2) [3-5, 11].

Table 1. Prevalence of anticardiolipin (aCL), glutamic acid decarboxylase (GAD) and antinuclear (ANA) antibodies in epileptic patients and controls [3-5, 11, 18]

	Epileptic patients as a whole (*n*=74)	**Seizure-free patients (*n*=52)**	**Therapy-resistant epileptic patients (*n*=22)**	**Controls (n=50)**
aCL +	20 (27.02%)*	14 (26.9%)	6 (27.3%)	5 (10%)
aCL -	54 (72.98%)	38 (73.1%)	16 (72.7%)	45 (90%)
GAD+	4 (5.4%)	3 (5.7%)	1 (4.5%)	2 (4%)
GAD-	70 (94.6%)	49 (94.3%)	21 (95.4%)	48 (96%)
ANA+	22 (29.7%)**	15 (28.8%)	7 (31.8%)	5 (10%)
ANA-	52 (70.3%)	37 (71.2%)	15 (68.2%)	45 (90%)

*P<0.037 vs. control values; **P<0.036 vs. control values

Table 2. Prevalence of antibodies according to type of epilepsy [3-5,18]

Type of epilepsy	**Generalized epilepsy (*n*=35)**	**%**	**Localized epilepsy (*n*=39)**	**%**
aCL +	11	31.4	9	23.0
GAD +	2	5.7	2	5.1
ANA +	12	34.2	10	25.6

In another recent study by Eriksson et al. a set of various autoantibodies in 50 consecutive children with epilepsy and in 20 healthy control subjects was analyzed [12]. None of the children had any clinical signs of immune system disorders. Results showed a significantly (P=0.011) higher prevalence of antiphospholipid antibodies in the study group (44%), as compared with the controls (10%). These antibodies were unexpectedly common (71-80%) in children with multiple-seizure types, often associated with symptomatic etiology, early onset and high frequency of seizures. There was no evidence of the antiphospholipid positivity being induced by certain antiepileptic drugs (e.g. phenytoin or carbamazepine). Even though the significance of

these autoantibodies remains unknown, their increased prevalence indicates that immune system mediated mechanisms may play a role in the manifestation of epilepsy in some children [12-14].

Peltola et al. and Cimaz et al. [15, 16] also showed an increased prevalence of autoantibodies in patients with epilepsy and stronger association with epilepsy than with antiepileptic drugs, indicating that immune dysregulation might be commonly associated with epilepsy. Frequency of antinuclear antibodies, anti-β2-glycoprotein I antibodies, and anticardiolipin antibodies were evaluated in groups of patients with therapy-resistant localization-related epilepsy, patients with generalized epilepsy syndromes and patients with a newly diagnosed seizure disorder without antiepileptic medication, and a group of healthy controls. Compared with the controls, the newly diagnosed patients had a significantly greater prevalence of immunoglobulin (Ig) G class anticardiolipin antibodies (21% versus 7%). The prevalence of IgM class anticardiolipin antibodies was significantly greater in all seizure groups (60% in localization-related epilepsy, 42% in generalized epilepsies, and 33% in newly diagnosed patients), as compared with controls (7%). Antinuclear antibodies were significantly more common in the newly diagnosed patients (21%) and localization-related epilepsy (24%), when compared with the controls (12%). When the patients with generalized epilepsy (8%) were used as a reference group, antinuclear antibodies were also significantly more frequent in localization-related epilepsy (relative risk [RR] = 2.9, 95%, confidence interval [CI]: 1.1 to 8.2) and newly diagnosed seizures (RR = 3.4, 95%, CI: 1.2 to 9.3).

Conclusions

Etiology and pathogenetic mechanisms of epileptic seizures are still insufficiently understood. In general it is perceived imbalance between activating and inhibiting processes as a result of dysfunction of ion channels and neurotransmitters - gamma aminobutyric acid (GABA), glutamate and aspartate. In many recent studies it is proved that most of the children with idiopathic form of epilepsy without clinical or serological markers of connective tissue disease, have elevated titers of various autoantibodies [2, 4, 8, 11], which cause immune-mediated neuronal damage. Moreover, in experimental studies it has been shown that antibodies can disrupt neuronal function by direct action on nerve terminals [17] and can reduce GABA receptor-mediated chloride currents, suggesting a direct and reversible mechanism through which they might lower seizure threshold [19-21]. It has also been postulated that antibodies to endothelium may induce apoptosis within the CNS [10, 22].

The role of immune mechanisms in the pathogenesis of epilepsy suggests the need for clarification and compliance with the immunological status regarding the presence of antinuclear and antiphospholipid, as well as other autoantibodies in the course of treatment, and an opportunity to apply immunomodulating therapy for better control on the incidence and severity of attacks [23]. Further investigations are needed for better estimation the correlation of age, sex, age at the onset of epilepsy, type and duration, seizure frequency, antiepileptic medications and presence of autoantibodies.

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