

Autoimmunity and Epilepsy in Children

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Abstract

Objective of this paper is to investigate whether autoantibodies are present in a cluster of patients with epilepsy. In 3 out of 88 epileptic patients, in whom no metabolic, bacterial, viral or malformative origin was demonstrated, the Authors showed the presence of antibodies to thyroid microsomes in 2, to nucleus (ANA) in 2, to glutamic acid decarboxylase (GAD) in 1, to transglutaminase in 1. In 2, reduced seizures by immunomodulant therapy were observed. The autoantibodies may have played a role in the pathogenesis of epilepsy, as demonstrated by positive results of the immunomodulant therapy. On the basis of the results the Authors suggests the need to search autoimmunity in every case of epilepsy.

Introduction

Epilepsy may be a feature of many neurological disorders, often with an unknown aetiology. Some cases of epilepsy are resistant to therapy (i.e. they present with one or more seizures per month, despite adequate treatment) [1]. Recently, some types of epilepsy have been ascribed to an inflammatory mechanism (for example, Rasmussen epilepsy). In many cases of epilepsy, raised interleukins (mainly IL1 β and TNF α) suggest an inflammatory origin. In man, CNS inflammation involves both innate (phagocytes and microglia) and adaptive (B and T lymphocytes) immune systems, in which communication between cells may occur (via cell to cell contact or via cytokines) [2]. Experimental studies in mouse showed that brain inflammation may increase neuronal excitability and blood-brain barrier (BBB) permeability, which contributes to seizures in some conditions. In children, malformations, infections, neoplasias of CNS are responsible of epilepsy; recently, some cases of epilepsy have been ascribed to autoimmunity (i.e. to immunity against a self-antigen) [2].

Possible immunological mechanisms in epilepsy were reported in three main areas: 1) childhood epilepsy syndromes; 2) epilepsy associated with immunological diseases; 3) unselected epileptic patients [3]. In these conditions, specific antibodies (abs) may be associated with epilepsy through a possible pathogenetic mechanism. The pathogenetic importance of these antibodies is supported by the positive results of immunomodulatory treatment (ACTH, cortisone, immunoglobulins) or of specific diet (gluten intolerance/ceciac disease). In paediatric epilepsy, antibodies as markers of CNS autoimmunity have been reported. Anti-voltage gated potassium channel (VGKC) abs are present in epilepsies associated with limbic or other encephalopathies. VGKC abs are antibodies targeting protein antigens of surface cells, KV1 is a complex that is critical for regulatory neuronal excitability [4]; anti-glutamic-acid decarboxylase antibodies (anti-Gad), are antibodies against an enzyme that catalyzes the conversion of glutamate to gamma-aminobutyric acid. These abs are sometimes associated with epilepsy (GAD-positive epilepsy), a pathological condition often involving temporal lobe, cerebellum and brainstem, but are also present in stiff person syndrome, diabetes and pernicious anemia. GAD 65 abs are markers of cytotoxicity T-cell. Antithyroideal abs may interest the CNS in the context of a different autoimmune disorder. Antimicrosomal, anti-peroxidase, antithyreoglobulin abs are associated with thyroiditis and, if concomitant with neurological symptomatology, epilepsy, psychic disturbances, confabulations, hallucinations and/or depression, permit a diagnosis of Hashimoto encephalopathy. A direct [3] antibody effect, possibly due to common brain/thyroid antigen, is postulated in this case [5]. Anti trans-glutaminase and anti-endomysium antibodies are sometimes present in epilepsy associated with gluten intolerance/ceciac disease, an immune-mediated disease of small bowel triggered by gluten in genetically predisposed individuals [6]. Anti nuclear antibodies (ANA) are present in some epileptic patients but are of uncertain pathogenetic significance in epilepsy [7]. ANA are sometimes associated with anti-cardiolipin and/or anti-phospholipid antibodies in patients with lupus erythematosus and epilepsy [3]. In epilepsy, ANA are frequent (25,2%) but not related to the type of epilepsy [7]. The significance of ANA in sera of epileptic patients receiving treatment is doubtful [7] and according to some AA, [7, 8], they are attributable to antiepileptic drugs. ANA

have been reported in systemic lupus erythematosus as a possible cause of epilepsy in this disease [3].

In a personal research the presence of some auto-antibodies was demonstrated in three of 88 epileptic patients, in whom the possible viral, bacterial, metabolic, or malformative origin was excluded. These cases are described as follows.

Materials and Methods

Patient 1, now 37 years old. Family history showed systemic lupus erythematosus in the grandmother and arthritis with low IgA in the mother. From 7 months of life the male proband presented severe myoclonic epilepsy of infancy (SMEI), recurrent seizures (1-2 every day) and status epilepticus. EEG, initially normal, showed subsequently slow waves and, at 2 years of age, diffuse slow waves and spikes. A variant of SCN1A gene (IVS1+5 G/A) in intron 1 was demonstrated. From the first year of life, lymphocytosis (relative count 92% absolute count 10,129/mm³) and neutropenia (relative count 5% and absolute count [a.c.] 550/mm³) were recorded. At 3 years of age WBC were 6,200 (N=16%; L 82%, M 2%) and at 7 they were 6,900 (N29%, absolute count 2,001; L 65% a.c.4485; M=6%). IgA were raised. Diagnosis of a lymphoproliferative syndrome was made. Mental retardation mainly affected language development. At 21 years of age, ANA antibodies (I:20) and circulating immuno-complexes (13 mg/dl; VN<4) were present in blood. IgA were raised; compensated hypothyroidism (TSH: 4.5 µU/ml; n.v. 0.23-4; T4=4.3; NV=5 microg/ml) with reduced volume of the thyroid gland were recorded. Anti-cardiolipin and anti-dsDNA antibodies were negative. A diagnosis of autoimmune thyroiditis was made. At 25 years of age, arthritis, raised ESR (50; NV<10), positive ANA (I:160-I:320), elevated IgA, positive CRP (8.6; NV<2) were reported. Evidence of cancer was not present. NMR showed mild cerebral cortical atrophy. At 28 years of age, anti-thyroidal microsomal, anti-transglutaminase, anti-endomysium and anti GAD antibodies were negative. Skin biopsy showed lymphomonocytoid perivascular cuffing and a junctional nevus; immunofluorescence showed, IgM granular accumulation at the dermo-epidermal junction. A diagnosis of autoimmune lymphoproliferative syndrome with myoclonic epilepsy was made.

Cortisone therapy reduced seizures (1 per week), improved arthritis and lymphoproliferation. SMEI is attributed in about 70% of cases to SCN1A mutation [9]. Thyroiditis and arthritis are autoimmune disorders characterized by multiple antibodies: ANA and microsomal abs were present in our case with SMEI and may have contributed to worsening of the epilepsy. This hypothesis is supported by clinical picture, laboratory results, and response to corticosteroids.

Patient 2, 7 years old. The second patient was a male, born to unrelated parents at term of an uncomplicated pregnancy. At birth, the patient presented with dysmorphic facial features and cryptorchidism and, at three months of age, he had onset of epilepsy with repetitive seizures of tonic-clonic type. Fenytoin, valproate and other

antiepileptic drugs were ineffective and a diagnosis of "epilepsy resistant to anti-epileptic drugs" was made. Subsequently, the boy suffered from infantile spasms, hypsarrhythmia and absences which suggested the diagnosis of West syndrome. In the following years, seizures were reported. EEG recorded multiple spikes and waves and diffuse theta waves. Cerebral CT was negative. Urography showed left kidney ptosis with bilateral cysto-ureteral reflux. Physical examination at 7 years of age showed left hemiparesis, diffuse hypotonia, ataxia, retarded psychic development. NMR demonstrated cerebellar vermis hypoplasia and atrophy of subtentorial structures.

Assays of anti-microsomal thyroideal and anti-thyreoglobulin, anti-endomysium and anti-insulin antibodies were normal. Anti-glutamic acid decarboxylase antibodies were 2.2 IU/ml (nv<1). IgG 1,582 mg/dl (NV 506-1,560), insulinemia 3.8 microU/ml (nv 6-27). ACTH therapy caused disappearance of seizures, amelioration of ataxia and EEG. Some patients with antiepileptic drugs resistant epilepsy had GAD-positive antibodies. The finding of raised blood levels and positive intrathecal synthesis of GAD antibodies in epileptic patients, suggested the possible autoimmune pathogenesis of GAD-positive epilepsy [10, 11].

Epilepsy associated with GAD abs encompasses a wide spectrum of epilepsy syndromes (temporal lobe epilepsy, epilepsy with cortical dysplasia, juvenile myoclonic epilepsy). In mouse, low levels of GABA are associated with status epilepticus provoked by drugs; in man, seizures in patients positive for GAD ab may be explained by interference with GABA, an inhibitory neurotransmitter. Reports of seizures, responsive to GABA-ergic agonists (benzodiazepines, sodium valproate, cortisone) and to plasmapheresis suggest a possible causative role of anti-GAD antibodies [3, 12]. In our case, the possible role of GAD ab in the pathogenesis of epilepsy was suggested by the clinical and EEG amelioration of the disease by treatment with ACTH. Alternatively, GAD-positive epilepsy may be related to a (pre)diabetic condition: serum samples from patients with insulin-dependent diabetes associated with neurological disease stain the cytoplasm of the rat cerebellar granular layer *in vitro*, whereas those from patients with uncomplicated diabetes do not stain the cytoplasm [10, 12].

Patient 3, 13 years old. The third patient presented with learning and language difficulties, in particular dyslexia and dysgraphia from the first years of life. At 13 years of life, the boy presented with epilepsy focus of spikes in right temporal lobe and motor incoordination. Anti-transglutaminase and anti-endomysium antibodies were positive (53 U; nv<7). Duodenal biopsy showed villous atrophy, cryptal hyperplasia and raised lymphocytes in epithelium of the duodenal mucosa. Diagnosis of celiac disease with epilepsy was made. Gluten elimination from the diet was followed by amelioration of motor incoordination, language disturbances, and EEG records. In celiac disease, it was recently suggested that molecular mimicry (i.e. epitopes shared between deaminated gliadin and transglutaminase 2) could play a role in antibody production [6]. In brain parietal sections of a patient with gluten intolerance, an accumulation of endomysium

type IgA, antitransglutaminase 2 abs was demonstrated with vascular cuffing of T lymphocytes, not present in the brain of a control without gluten intolerance [13]. It is now accepted that gluten intolerance/ceeliac disease is a systemic illness that may appear in a range of tissues and that gluten sensitivity is an autoimmune disease with different manifestations [13], sometimes associated with epilepsy. Autoantibodies targeting the brain and intestinal transglutaminase could be responsible of gluten ataxia and epilepsy [13, 14].

All these data suggest the possible causative role of gluten in this case of epilepsy.

Conclusions

In 3 out of 88 epileptic patients, we demonstrated the presence of different antibodies (to thyroid microsomes in 2, to nuclei in 2, to GAD in 1, to transglutaminase and to endomysium in 1). The presence of these antibodies may have played a role in the pathogenesis of epilepsy and contributed to the choice of immunomodulant therapy. In our cases, autoimmunity may have aggravated the epileptic symptomatology. Alternatively, the autoantibodies may have been an epiphenomenon, attributable to antiepileptic treatment, and the epilepsy due exclusively to an independent abnormality. Further studies are necessary, however our experience suggests the need to search for autoimmunity in every case of epilepsy.

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