

Original article

Antiphospholipid antibodies in children and adolescents with epilepsy

Background: Some immunologic mechanisms of epilepsy are cited in literature. The possibility that epilepsy might be associated with the production of autoantibodies has not been sufficiently addressed.

Objective: This study investigates the prevalence of some antiphospholipid antibodies in pediatric primary epilepsy in relation to the type of seizures, the duration of the disease and the antiepileptic drugs received.

Methods: The study included 37 patients in the pediatric age groups with epilepsy (30 with idiopathic epilepsy and 7 with cryptogenic epilepsy); 10 of them were newly diagnosed in comparison to ten healthy children. The patients were subjected to clinical, laboratory and radiologic evaluation to verify the diagnosis and to exclude thrombotic or autoimmune collagen disorders. Anticardiolipin IgG and IgM and anti- β_2 -glycoprotein I IgG and IgM antibodies were measured in all subjects using the ELISA technique.

Results: Forty percent of the patients were positive for at least one of the antiphospholipid antibodies and 16% displayed more than one antibody in their serum. The mean values of anti CL IgG and anti β_2 GP I IgM were significantly higher in the patients (mean 11.32 ± 6.3 GPL and 4.43 ± 2.8 U/ml, respectively) as compared to the control group (mean 5.25 ± 1.9 and 1.6 ± 0.6 , respectively) ($P < 0.001$). The concentrations of the tested antibodies were comparable among patients with focal compared to those with generalized seizure, or in patients with idiopathic compared to cryptogenic epilepsy. Patients with newly diagnosed untreated epileptic seizures showed a substantial prevalence of antiphospholipid antibodies. They even demonstrated significantly higher mean values of a β_2 GP I IgG (10.7 ± 11 GPL) and a β_2 GP I IgM (5.8 ± 3.0 U/ml) when compared to the rest of the patients (mean 5.9 ± 3.5 and 3.9 ± 2.6 respectively). There seem to be no effect of the different antiepileptic drugs or the degree of seizure control on the development of antiphospholipid antibodies.

Conclusions: The antiphospholipid antibodies seem to be present at a higher rate in pediatric patients with epilepsy. The increased prevalence of those autoantibodies is associated with epilepsy regardless of the type of seizures, the antiepileptic drugs used or the degree of seizure control, suggesting that immune dysregulation may be linked to the pathogenesis of primary epilepsy.

Key words: anti β_2 glycoprotein ; anticardiolipin; antiphospholipid; epilepsy; immune system.

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INTRODUCTION

The occurrence of antinuclear antibodies and lupus like syndromes in patients with epilepsy has traditionally been regarded as a consequence of antiepileptic drugs. However, in the recent years, the role of autoimmunity in the pathogenesis of epilepsy has been the focus of many studies¹. Autoantibodies such as those directed against the GM1 ganglioside² and antibodies against the GLUR3 receptor subunit³ have been reported in the sera of patients with epilepsy, but the possibility

that epilepsy per se might be associated with immunologic alterations and the production of autoantibodies has not been sufficiently addressed. Several studies have reported high percentages of antiphospholipid (aPL) antibodies in patients with epilepsy^{4,5,6}. However, it is still not clear if these autoantibodies are only an epiphenomenon or whether they have a true pathogenic role.

The aim of this study was to investigate the expression of antiphospholipid antibodies [anti β_2 glycoprotein I (IgM and IgG) and anticardiolipin

antibodies (IgM and IgG)] in pediatric patients with primary epilepsy and to find out whether they have any relation to the type of seizures, duration of the disease or the antiepileptic drugs used to achieve disease control.

METHODS

The present study was carried out at the Neurology Unit of the Children's Hospital of Ain Shams University in the period from November 2002 to June 2003. It included 37 children and adolescents diagnosed with primary epilepsy and are regular attendees of the Unit's Clinic, and the sample was enrolled consecutively. They were 23 males and 14 females and their ages ranged between 2 to 16 years with a mean of 7.4 ± 4.0 years.

For comparison, a control group of ten clinically healthy children matching the patients in age and sex were recruited in the study. They were 6 males and 4 females, with ages ranging between 2 and 15 years and a mean age of 8.1 ± 3.5 years. The local ethical committee approved the study and consents were taken from the parent(s) of the enrolled subjects.

Inclusion criteria of the patients:

- Patients with no evidence of definite remote cause for epilepsy, that is patients with primary epilepsy. According to the recommendations of International League Against Epilepsy⁷, most of our patients were diagnosed as having idiopathic epilepsy; only 7 patients had cryptogenic epilepsy.
- Patients with normal liver function tests, renal function tests, blood picture, electrolytes, blood glucose, metabolic screen and neuroimaging of the brain.

Exclusion criteria of the patients :

- Patients with history or investigations that confirmed a remote and definite CNS insult that underlies the epilepsy syndrome i.e. patients with symptomatic epilepsy.
- Any patient whose medical history, examination or laboratory investigations could suggest autoimmune pathology or previous thrombosis.
- Patients with current infection till cured.

Included patients were subjected to the following:

1-Clinical evaluation: Detailed history was taken from each patient by interviewing him and the parents and by examining hospital records, laying stress on the patient's age, duration of epilepsy, type of the seizure disorder and seizure frequency. Twenty-seven patients were on regular antiepileptic drug therapy (AED), while ten were enrolled as having newly-onset idiopathic epilepsies. These were

included within one month of onset of symptoms; none was on therapy at the time of evaluation. The AEDs received and the degree of seizure control were included. The disease was considered controlled if there were no seizures for at least 4 months prior to enrollment. Patients were carefully examined laying stress on the neurologic examination and features of autoimmune disorders.

2-Investigations:

- Laboratory investigations needed for diagnosis and follow up were performed; for e.g. complete blood count using coulter counter (T660, USA), hepatic and renal function tests, serum levels of calcium, sodium, potassium and fasting blood glucose using Synchro CX5 system (Beckman Inst., California, USA).
- Interictal wake and sleep EEG tracings with photic and (whenever possible) hyperventilation provocation were performed for all patients (Telefactor, PA, USA). Neuroimaging studies (CT brain and in some cases magnetic resonance imaging (MRI) of the brain) were done as well (MR-max 500, Genenral Electric, USA).
- Anticardiolipin (IgG and IgM) were measured for the patients and the control groups using ELISA technique (Reads Medical Products, Colorado, USA). Results were obtained by reading the optic density (OD) absorbance using a spectrophotometer. Calibrator sera were provided, with the aCL concentration expressed in IgG phospholipid (GPL) or IgM phospholipid (MPL) units, according to the recommendations developed at the workshop on standardization and interpretation of anticardiolipin test results⁸. The O.D. values of all the other samples were multiplied by the conversion factor to obtain aCL antibody concentrations in standard units. Results were considered positive for the studied antibody if the aCL values were ≥ 23 GPL for IgG and ≥ 11 MPL for IgM antibodies.
- Anti- β_2 -glycoprotein I (IgG and IgM) were measured by indirect solid phase enzyme immunoassay (Orgentec Diagnostika GmbH, Mainz, Germany)⁹. It is designed for the quantitative measurement of IgG or IgM class autoantibodies directed against β_2 -glycoprotein I. For anti- β_2 -glycoprotein I IgG and IgM a 4-Parameter-Fit with lin-log coordinates for optical density and concentration is the data reduction method of choice. Results were considered positive if anti- β_2 -glycoprotein I values were > 8 U/ml, borderline if 5-8 and normal if < 5 U/ml.

Statistical analysis:

Data were analyzed by a standard computer program using IBM (SPSS for windows). Results

were expressed as mean \pm SD or %. The Chi Square test (χ^2) was used to discriminate the difference in descriptive laboratory data. The t test was employed in comparing the numerical data of different patient groups. Correlation of different numerical variables was attempted using Spearman r correlation coefficient test. From statistical tables, the probability (p) values were calculated; p values less than 0.05 were considered significant.

RESULTS

Clinical features of the included patients are summarized in Table (1). The mean disease duration was 3.3 ± 2.5 years, ranging from one month to 9 years. Ten of the included patients had newly diagnosed epilepsy. According to detailed history and EEG findings, 12 patients were classified as having generalized seizures and 25 patients as having focal seizures (with or without secondary generalization). According to the presumed etiology, 30 patients were classified as having idiopathic epilepsy syndromes and 7 as having cryptogenic syndromes, all of the latter group with focal seizures.

Anticardiolipin (aCL) IgG antibodies were detected at a value higher than 23 GPL units in 2 (5.4%) of the 37 patients, while anticardiolipin IgM antibodies were detected at a value higher than 11 MPL units in only one (2.7%) patient. None of the control sera was positive for anticardiolipin antibodies.

Anti β_2 -glycoprotein I (β_2 GP I) IgG antibodies were positive in 13 (35.1%) patients, borderline in 12 (32.4%) and negative in 12 (32.4%) and were positive in 10% of the control sera and borderline in 40% of them. On the other hand, anti β_2 glycoprotein I IgM antibodies were positive in 18.9% (7 patients), borderline in 13.5% and negative in 67.6% of the patients and were negative in all the control sera (Figure 1).

The mean aCL IgG in the patients group (mean = 11.32 ± 6.3 GPL) was significantly higher than the controls (mean = 5.25 ± 1.9 GPL) ($t=5.51$, $p<0.0001$), while there was no statistically significant difference between cases and controls as regards the mean aCL IgM (mean = 3.81 ± 1.8 and 4.21 ± 2.0 MPL, respectively). On the other hand, the mean β_2 GP I IgM values showed a significantly higher value among patients (mean = 4.43 ± 2.8 U/ml) compared to controls (1.6 ± 0.6 U/ml) ($t=4.9$, $p<0.0001$), while there was no significant difference in the values of β_2 GP I IgG when comparing both groups (mean = 7.21 ± 6.6 and 5.51 ± 1.9 U/ml, respectively) (Figure 2).

Patients with generalized seizures were comparable to those with focal seizures in terms of the mean values of antibodies tested or their positivity rates. The same was observed on comparing patients with idiopathic to those with cryptogenic epilepsy.

Sixty percent of patients with newly diagnosed epilepsy showed positivity for at least one of the tested antibodies [anticardiolipin antibodies IgG (10%), anti β_2 glycoprotein I IgG (50%), and anti β_2 glycoprotein I IgM (30%)]. They also showed significantly higher mean values of β_2 GP I IgG (10.7 ± 11 U/ml) and β_2 GP I IgM (5.8 ± 3.0 U/ml) when compared to the rest of patients (mean 5.9 ± 3.5 , 3.9 ± 2.6 U/ml respectively) ($t= 2.2$ and 2.08 , $p= 0.03$ and 0.04 , respectively). The mean values of aCL (IgG or IgM) antibodies showed no significant difference in between both groups (Figure 3).

There was no statistical difference between patients on valproate and those on carbamazepin or between patients on monotherapy and those on polytherapy in the mean values of antibodies tested or their positivity rates. Moreover, the antibody results were not influenced by achievement of seizure control in the studied sample.

The concentrations of the studied antibodies did not correlate to the age of patients, age at onset of the disease, its duration, or the frequency of the seizures.

Table 1: Clinical data of the patients group

Variable	Results
Gender [no (%)]	
Male	23 (62.2%)
Female	14 (37.8%)
Age [mean \pm SD]	7.4 ± 4.0
Family history of epilepsy [no (%)]	
Negative	30 (81.1%)
Positive	7 (18.9%)
Type of seizures [no (%)]	
Generalized	12 (32.4%)
Focal	25 (67.6%)
Age of onset in years [mean \pm SD]	4.4 ± 3.9
Duration in years [mean \pm SD]	3.3 ± 2.5
Type of seizures [no (%)]	
Idiopathic	30 (81.1%)
cryptogenic	7 (18.9%)
AEDs [no (%)]	
Mono therapy	23 (85.2%)
valproate	11 (47.8%)
carbamazepin	12 (52.2%)
Poly therapy	4 (14.8%)
Control of seizures [no (%)]	
Controlled	17 (63.0%)
Uncontrolled	10 (37.0%)

AEDs: antiepileptic drugs ; no: number.

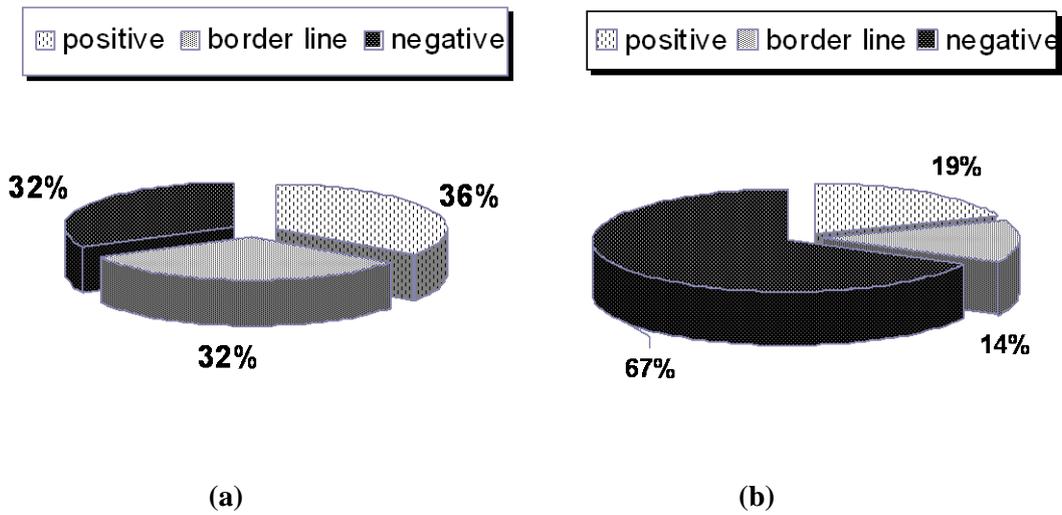
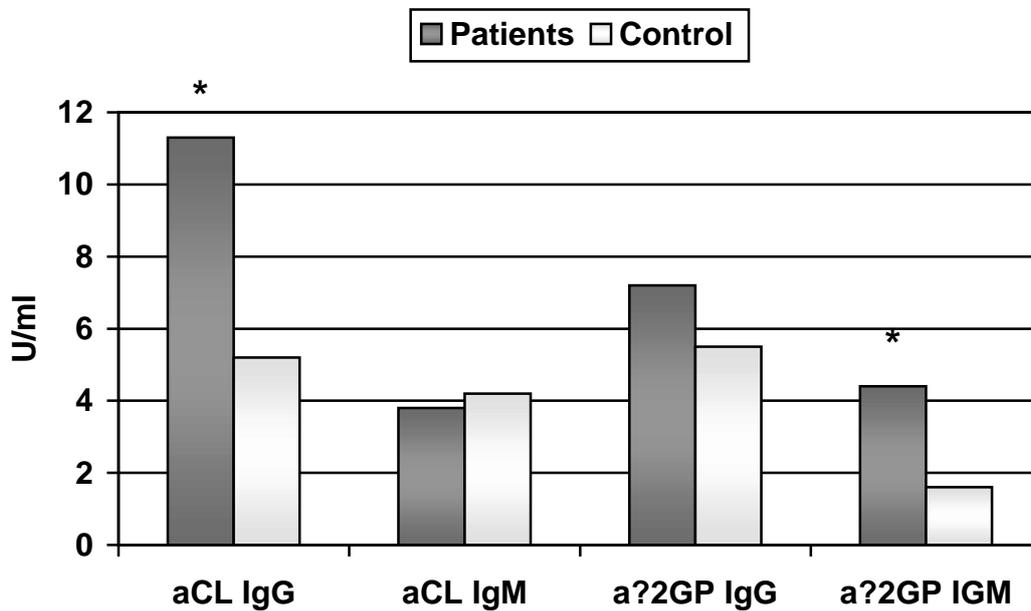
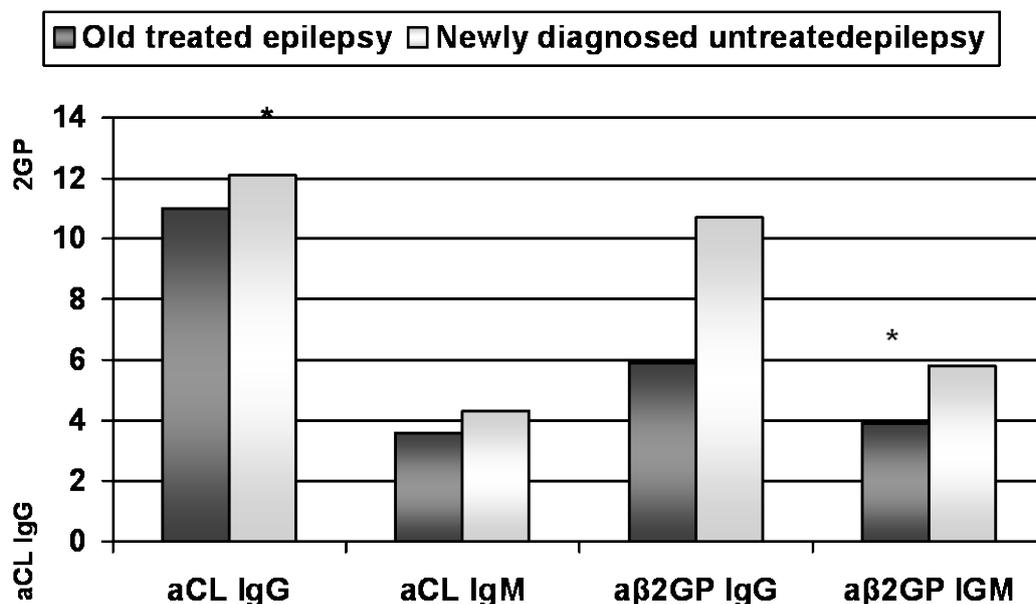


Figure 1: Percentage of patients with positive anti β₂ glycoprotein I IgG (a) and IgM (b) among the studied cases.



anti β₂GP I : anti β₂ glycoprotein I; anti CL: anticardiolipin.
 *p<0.05 (Significant)

Figure 2: The mean values of aCL IgG (GPL) and IgM (MPL) and aβ₂GP I IgG and IgM (U/ml) in the studied sample



anti β_2 GP I : anti β_2 glycoprotein I; anti CL: anticardiolipin.

* $p < 0.05$ (Significant)

Figure 3: Variation of the mean values of aCL IgG (GPL) and IgM (MPL) and a β_2 GP I IgG and IgM (U/ml) with the disease state at enrollment.

DISCUSSION

Ischemic events such as focal cerebral ischemia are the most common neurologic disorders associated with aPL antibodies; however, cognitive dysfunction, depression, migraine, chorea and seizures have all been associated with aPL antibodies¹⁰. Recently, it has been suggested that interaction between aPL antibodies and central nervous system cellular elements rather than aPL - associated thrombosis seems to be a more plausible mechanism for these clinical manifestations^{11,12,13}.

The present work was carried out to investigate the prevalence of antiphospholipid antibodies (anti β_2 glycoprotein I and anticardiolipin antibodies) in a group of pediatric patients with epilepsy and the possible association with the primary type of seizure, its duration or the type of antiepileptic drugs received. We noticed that 40.5% of the patients were positive for at least one of the antiphospholipid antibodies and several patients (16%) displayed more than one antibody in their serum, though none of our patients had evidence of thrombosis or autoimmune disease. The aCL IgG was considered positive in 5.4% of our series with a mean that was significantly higher among patients in contrast to aCL IgM, which showed no significant difference between patients and controls.

On the other hand, the mean a β_2 GP I IgM was significantly higher among patients, while a β_2 GP I IgG showed no significant difference between patients and controls.

Verrot et al.⁴ found a prevalence of 19% of aCL antibodies, in patients with epilepsy, values that were significantly higher than their control group, though none of their patients revealed clinical symptoms of SLE, or clinical features of primary antiphospholipid antibody syndrome (APS). Similar to our results, it was the IgG isotype that showed significant difference from the control results, while the IgM aCL antibodies were not detected at a significant value. Eriksson et al.¹⁴ and Pardo et al.⁵, in their studies on patients with epilepsy, reported even a higher prevalence (44% and 42%, respectively) of aPL antibodies. Eight of out nine cases of benign infantile convulsions, studied by Yoshimura et al.¹³, were positive for aCL IgG and the values of aCL IgG decreased over long term observation in three of these cases. Based on these data, they suggested that some immunological responses may be responsible for the pathogenesis of benign infantile convulsion.

The real pathogenic significance of aPL antibodies in epileptic patients is still unclear. Although it has been claimed that aPL antibodies are specific for

thrombosis-mediated antiphospholipid events, there is evidence that they also bind to brain tissue¹¹. IgG from patients with antiphospholipid syndrome were found to induce depolarization of brain synaptoneuroosomes in animal models, suggesting the possibility of a direct and reversible mechanism through which antiphospholipid antibodies might lower the seizure threshold¹⁵. Meroni et al.¹⁶ demonstrated that human brain microvascular endothelial cells bind higher amounts of β_2 GP I and can be activated by IgG from aPL positive sera and by $\alpha\beta_2$ GP I antibodies. In addition, β_2 GP I was identified immunohistologically on brain cells¹¹, and functional central nervous system involvement was reported in experimental models of antiphospholipid syndrome¹⁵. Altogether, these findings suggest a pathogenic role for aPL antibodies in epilepsy, by means of microinfarcts secondary to ischemic events, or by an immune mediated mechanism directed against endothelial or neuronal cells, as suggested in experimental models. We cannot argue strongly for the presence of epileptogenic cerebral ischemic lesions, a mechanism that is frequently invoked. Imaging of the brain found no ischemic lesion in our patients, however small microinfarcts not visible by imaging could not be excluded. The aCL antibodies could also reflect a common, perhaps genetically determined predisposition¹ to develop epilepsy and to produce autoantibodies as seems the case for aCL antibodies in schizophrenia¹⁷. Another putative mechanism might be through an autoimmune reaction to antigens expressed specifically by neurons that have an epileptic activity, as has been demonstrated for several types of seizure-induced genes¹⁸ or cell products¹⁹. Antiphospholipid antibodies associated with drugs have also been described²⁰.

Although no enough criteria for drug-induced aCL antibodies have been defined, they are usually of the IgM isotype, the IgG class aCL antibodies being negative or low in titer²¹. In the present study, aCL antibodies were of the IgG isotype. Whatever the mechanism by which the aPL antibodies appear and whatever their precise connection with epilepsy might be, the risk of thrombotic events and its primary prevention must be considered. Indeed, it is known that aPL antibodies, even when they are induced by drugs, significantly increase the risk of both venous and arterial thrombosis²².

The type of seizures whether generalized or focal did not seem to influence the mean values or the positivity of the antibodies tested in our series. A similar observation was previously noted⁴. On the other hand, two other studies noted that the

prevalence of antinuclear antibodies and perhaps anticardiolipin antibodies is greater in patients with localized related epilepsies than those with generalized epilepsies^{14,23}. Eriksson et al.¹⁴ reported a positivity of 13% for aPL in children with partial epilepsy and they suggested that these antibodies may indicate that an immune-mediated neuronal damage could be a pathogenic mechanism for partial epilepsy.

Our patients with idiopathic epilepsy demonstrated comparable concentrations and positivity rates of aPL antibodies to those with cryptogenic epilepsy. Another study reported that the cryptogenic group of patients with epilepsy is more presented among aPL antibodies-positive patients than the idiopathic group⁶. This may be due to the difference in the type of aPL antibodies they investigated, which are the antiprothrombin antibodies beside $\alpha\beta_2$ GP I and aCL.

A substantial prevalence of aPL (aCL and anti- β_2 glycoprotein I) (60%) was noticed among patients with newly diagnosed, untreated epileptic seizures in our series, which reinforces the concept that the occurrence of autoantibodies cannot be due to antiepileptic medications alone. Also, there was a significantly higher mean values of anti β_2 glycoprotein I IgM and IgG among those new cases when compared to the rest of the patients. In agreement with our data, Peltola et al.²³ reported a significant increase in anticardiolipin antibodies, anti β_2 glycoprotein I antibodies, and antinuclear antibodies expression among patients with newly diagnosed, untreated epileptic seizures. Thus, it seems that aPL antibodies could be more linked to the disease itself than to the medications received.

Again, there was no significant difference in the levels of antibodies tested among patients on monotherapy in comparison to those receiving polytherapy, neither did the results vary with the use of different antiepileptic drugs. Similar observations were cited in literature^{4,6}. The finding that aPL antibodies were even higher in patients with new onset seizures is supported by the study of Yoshimura et al.¹¹ who noted a decrease in aCL IgG by follow up in 37% of patients with benign infantile convulsions. This might suggest a direct role of the aPL in the pathogenesis of epilepsy.

In the present study, seizure control did not significantly influence the expression of the antibodies tested. Our results might contradict with some previously published data on the association between aPL and multiple seizure types¹⁴ and frequency of seizures⁶. However, it is worth noting that both studies included symptomatic epileptic syndromes, a group that was excluded in our study.

Our findings might also be limited by the small sample size.

In conclusions, the aPL autoantibodies (a β 2GP I and aCL) were detected at a significantly higher rate in a group of pediatric patients with primary epilepsy than in a matched group of healthy children. The increased prevalence of autoantibodies is more strongly associated with the epilepsy itself than with its type, the antiepileptic drugs used or the degree of seizure control, indicating that immune dysregulation may be associated with epilepsy. Although a direct causal relation cannot be advocated at this level, a pathogenic role of these antibodies cannot be excluded and screening for these antibodies may help in early diagnosis of diseases with autoimmune background. We thus recommend follow up of patients with positive aPL antibodies for development of autoimmune disease or thrombotic events. A trial of alternative therapeutic approaches (immunomodulator drugs) should be considered in difficult cases or in patients not responding to specific antiepileptic therapy.

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