

SHORT COMMUNICATION

Association of anticardiolipin antibodies with epilepsy in children

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ABSTRACT

We investigated the association of anticardiolipin antibodies (aCL) with epilepsy development and characteristics in children. This prospective case-control study included 40 epileptic children and 40 sex- and age-matched controls. Epileptic children had higher levels of aCL compared to healthy controls (5.66 ± 5.41 versus 2.37 ± 2.28 ; p value = 0.001). The novel finding of elevated levels of aCL predicted response to IVIg therapy (p value = 0.009). Patients with normal EEG had lower levels of aCL compared to those with EEG abnormal findings (p value = 0.015). Patients with the combined type of epilepsy had statistically significant higher levels of aCL compared to other types (p value = 0.046). Also, aCL levels were correlated with seizure frequency (p value = 0.019). These results declare the possible involvement of such antibodies in the onset or pathogenesis of epilepsy. Screening for aCL may help in the timely diagnosis of epilepsy and initiation of appropriate treatment.

Keywords: Epilepsy; Anticardiolipin Antibody; Antiphospholipid Antibody; IVIG; Children; Seizure

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1. Introduction

Epilepsy is one of the most common diseases of the central nervous system (CNS) in which aberration of electrical pathways in CNS causes impairment of cognition and seizures. It is defined as follows: (i) diagnosis of an epilepsy syndrome, (ii) a single reflex (or unprovoked) seizure with a probability of more seizures with a recurrence risk of $\geq 60\%$ following two unprovoked seizures, arising during the next ten years, and (iii) at least two reflex (or unprovoked) seizures arising >24 h apart^[1]. Epilepsy is considered as the third most common disease among chronic brain disease affecting 0.5%–1.0% of the universal population^[2,3]. A recent systematic review estimated 19.8 cases of 1000 patients with epilepsy died each year^[4]. Although it is confirmed that a synchronized firing and improper hyper-excitability of a group of neurons cause epileptic seizures^[5,6], the precise factor that exerts such occurrence remains obscure. A class of autoantibodies named antiphospholipid antibodies (aPLs) bind the phospholipids on plasma membranes^[7,8] and have an important role in this obscure mechanism. Some of these antibodies have diagnostic utilities for disease with autoimmune pathogenesis, including anti- $\beta 2$ -glycoprotein I ($\beta 2$ -GPI) antibodies, anticardiolipin antibodies (aCL), and lupus anticoagulant (LA)^[7]. A number of previous studies have revealed the relationship between epilepsy and aCL in both pediatric^[9,10] and adult subjects^[11]. On the contrary, some studies showed no association between aPLs and epilepsy^[12–14]. Further

studies on this topic are needed with respect to the present controversy. In addition, the generalizability of much-published research on this issue is problematic, because the epilepsy prevalence and features are affected by geographical variables. To the best of our knowledge, there is no single study conducted on the Iranian population. In this work, we investigated the aCL/IgG level in epileptic children.

2. Objectives

In this work, we investigated the aCL/IgG level in epileptic children and analyzed its association with disease-related factors such as duration, frequency, and type of seizures, findings of brain MRI, EEG, and neurologic examinations, and response to IVIG therapy.

3. Patients and methods

This prospective case-control study was performed in the outpatient clinic of the Pediatric Neurology Center of Tabriz University Hospital, Iran, between July 2018 and April 2019. Inclusion criteria were as follows: (i) definite diagnosis of epilepsy of any etiology or type, and (ii) under 18 years old. The exclusion criteria were as follows: (i) acute infections, (ii) clinical immune system diseases (e.g., renal diseases, diabetes, psoriasis, coeliac disease, connective tissue, and rheumatic diseases), and (iii) postnatal vascular insults. 40 consecutive epileptic children and 40 sex- and age-matched controls were included. Controls were randomly selected among those who came to the outpatient clinic for routine pediatric examination, and chronic disorders that may change the autoantibody status were rolled out in them. A structured questionnaire was designed to record all demographic data, neurological diagnosis/symptoms, frequency of seizures during the last year, duration and type of epilepsy, antiepileptic drugs (AEDs) in use, and response to intravenous immunoglobulins (IVIg) therapy. Brain MRI and EEG were performed for all patients without any knowledge of laboratory findings. Patients underwent IVIg therapy four times in the first week and next once a week during the second, third, and sixth weeks. The last infusion was administered optionally as a booster in the sixth month. All cases also underwent classic AEDs. Patients were considered as responders to IVIg therapy if there was a 50% or

higher decrease in seizure frequency during the six months after the first IVIg therapy in comparison to that during the one month before getting included in the study. The patients were classified into three main groups of epilepsy according to the ILAE Guidelines, based on etiology and electroclinical findings^[15], including (i) focal, (ii) generalized, and (iii) combined. Clinical symptoms or signs of immune system diseases and acute infections, as well as any vascular disease, were looked for carefully. A pediatric neurologist (SS) performed all neurological and clinical examinations. The patients underwent a 1.5 Tesla brain MRI with a special epilepsy protocol that analyzed by expert neuroradiologists^[16]. Among several types of aPLs, we determined only the level of IgG class aCL. Results were expressed in international GPL (IgG phospholipid) units. We obtained about 20 mL of blood from both patients and controls, and the values >15 GPL were considered positive. The value was determined by In-house ELISAs based on the manufacturer's instructions and routine established laboratory methodology in the Center of Laboratory Medicine in the Department of Microbiology, Tabriz University Hospital, Iran. In summary, we coated cardiolipin onto an ELISA plate. After blocking with 10% bovine serum, we added diluted serum (1:50). Then, we added the alkaline phosphatase conjugated-secondary anti-IgG at 1:2000 dilutions (Jackson ImmunoResearch; West Grove, PA, USA). Next, the reactions were visualized with the substrate, with the intensity evaluated at 450 nm. The available variables for the control group were the level of antibody, sex, and age. Our study was approved by the Ethical Committee of Tabriz University of Medical Science. Informed consent was obtained from all cases or their parents. Data were analyzed using the SPSS version 23.0 for Windows. We expressed data as the mean value \pm SD or number (percentage) or number (percent). Correlations were determined using Spearman's rank correlation coefficient. We used ANOVA, Kruskal Wallis, Chi-Square, and Mann-Whitney U test. A *p* value < 0.05 was considered statistically significant.

4. Results

The patient group comprised 20 boys and 20 girls with a mean age of 5.93 ± 2.73 years. The control group consisted of 23 boys and 17 girls whose

mean age was 6.20 ± 2.32 years. The mean duration of seizures was 3.55 ± 1.96 years. In the patient group, 15 (37.5%) cases were on Sodium valproate, 9 (22.5%) on clobazam, 2 (5%) on zonisamide, 28 (70%) on phenobarbital, 15 (37.5%) on carbamazepine, 11 (27.5%) on levetiracetam, 1 (2.5%) on clonazepam, 4 (10%) on vigabatrin, and 1 (2.5%) on topiramate. There was a significantly higher value of IgG class aCL in patients compared with controls (5.66 ± 5.41 versus 2.37 ± 2.28 ; p value = 0.001). When we considered the value of 15 as the cut-off point for aCL, we found that all subjects with positive aCL (6 cases) came from the patient group (p value < 0.05).

There was not a statistically significant difference between girls and boys in the aCL level either in the patient group (5.51 ± 5.46 and 5.81 ± 5.49 , respectively; p value = 0.871) or controls (2.63 ± 2.09 and 2.07 ± 2.47 , respectively; p value = 0.181).

5 patients (12.5%) showed positive responses to IVIg therapy. There was a higher value of aCL in patients with positive responses to IVIg therapy compared with patients that did not respond (14.50 ± 6.42 versus 4.39 ± 3.94 ; p value = 0.009). This is the first reported such finding in the literature. There was a statistically significant correlation between the value of aCL and the duration of disease (p value = 0.025, correlation coefficient = 0.354).

Results of neurologic examination of patients are shown in **Table 1**. Patients with normal neurologic examination had the least value of aCL, vice versa, mental retard patients had the highest least value of aCL. However, the comparison of aCL among patients with several neurologic examination findings revealed no difference (p value = 0.176).

Table 1. Results of neurologic examination of patients ($n = 40$) and the value of aCL in each subgroup

	Frequency (%)	aCL/IgG
Normal	25 (62.5%)	4.25 ± 4.22
Hemiparesis	4 (10%)	5.57 ± 3.16
Mental retardation	5 (12.5%)	11.98 ± 8.49
Evolutionary delay	6 (15%)	6.30 ± 5.34

aCL/IgG: IgG class anticardiolipin antibodies.

MRI findings of patients and the value of aCL in each radiological subgroup are presented in **Table 2**. Patients with normal MRI had the least value of aCL, vice versa, patients with brain atrophy had the highest value of aCL; however, this difference

was not significant (p value = 0.336).

Table 2. MRI findings of patients ($n = 40$) and the value of aCL in each subgroup

	Frequency (%)	aCL/IgG
Normal	29 (72.5%)	4.70 ± 5.00
Brain atrophy	6 (15%)	10.33 ± 7.10
Basal ganglia involvement	1 (2.5%)	5.20
Late onset stroke	3 (7.5%)	4.10 ± 3.81
Born onset stroke	1 (2.5%)	7.25 ± 2.33

aCL/IgG: IgG class anticardiolipin antibodies.

EEG findings of patients are presented in **Table 3**. The comparison of patients with different EEG findings in the aCL levels showed a significant difference (p value = 0.015). Patients with normal EEG had the least value of aCL, vice versa, patients with Encephalopathy related to status epilepticus during slow sleep (ESES) had the highest value of aCL. **Table 4** shows the value of IgG class aCL in patients with several types of epilepsy. Patients with combined epilepsy had the highest value of aCL, and it was statistically significant (p value = 0.046).

The frequency of patients' seizures and their relationship with the aCL levels are presented in **Table 5**. Patients with high seizure frequency had a high value of aCL compared to those with low seizure frequency, and it was statistically significant (p value = 0.019, correlation coefficient = 0.368).

Table 3. EEG findings of patients ($n = 40$) and the value of aCL in each subgroup

	Frequency (%)	aCL/IgG
Normal	21 (52.5%)	3.46 ± 2.60
Burst suppression	1 (2.5%)	3.20 ± 2.90
ESES	2 (5%)	17.80 ± 3.67
Focal wave	1 (2.5%)	2.60 ± 1.80
Linkous	3 (7.5%)	9.20 ± 7.75
Focal spike wave	8 (20%)	7.56 ± 6.23
General spike wave	1 (2.5%)	5.30 ± 5.01
Spike wave + burst suppression	1 (2.5%)	3.70 ± 2.90
West syndrome	2 (5%)	7.65 ± 10.53

aCL/IgG: IgG class anticardiolipin antibodies; ESES: Encephalopathy related to status epilepticus during slow sleep.

Table 4. Different types of epilepsy in patients ($n = 40$) and the value of IgG class aCL in each type

	Frequency (%)	aCLs/IgG
Focal	20 (50%)	14.91 ± 4.65
Generalized	14 (35%)	4.59 ± 4.03
Combined	6 (15%)	10.63 ± 8.28

aCLs/IgG: IgG class anticardiolipin antibodies.

Table 5. Seizure frequency of patients ($n = 40$) during last year and the value of IgG class aCL in each subgroup

	Frequency (%)	aCL/IgG
Without seizure	26 (65%)	3.56 ± 2.55
1	2 (5%)	3.05 ± 1.06
2	4 (10%)	9.26 ± 7.44
>2	8 (20%)	10.11 ± 7.23

aCL/IgG: IgG class anticardiolipin antibodies.

5. Discussion

Our study had five main findings. First, epileptic children had higher levels of aCL compared to healthy controls. Second, elevated levels of aCL predicted response to IVIg therapy, which is novel. Third, patients with normal EEG had lower levels of aCL compared to those with EEG findings. Fourth, patients with the combined type of epilepsy had higher levels of aCL compared to other types. Fifth, patients with higher seizure frequency had higher levels of aCL.

Similar to previous studies^[11,17–19], the findings of our study indicated higher levels of aCL in epileptic children compared to healthy controls. A recent systematic review and meta-analysis reported positive aCL in 28.69% ($n = 358/1248$) of epileptic cases and 8.13% ($n = 65/800$) of healthy controls. Also, in this meta-analysis, a significant relationship between epilepsy and the elevated levels of aCL was reported (OR = 5.16, 95% CI: 3.21–8.28, p value < 0.00001)^[20]. A recent study conducted by Attilakos *et al.*^[17] on children with new-onset idiopathic epilepsy declared significant differences in aPLs levels between healthy controls and cases at the diagnosis and before initiation of treatment. They reported that 44% of cases had positive aPLs (either anti- β 2-GPI or aCL IgG) in comparison with 10% of healthy controls (p value = 0.019). In our study, the prevalence of positive aCL in the patient group and control group was 15.0% and 0.0%, respectively. The difference in the positivity rate for antibodies between studies may be caused by the difference in antibodies measured (aCL in our study and anti- β 2-GPI IgG versus aCL IgG in the study of Attilakos *et al.*^[17]). These results declare the possible involvement of such antibodies in the onset and pathogenesis of epilepsy. So far, the events contributing to epileptogenesis and seizure generation have still remained largely obscure. Evidence of recent experimental models of seizure and epilepsy

has suggested that glial cells and particularly astrocytes could have the central role in epilepsy development^[21,22]. Indeed, key changes contributing to circuit hyperexcitability in epileptic tissue seem to be highly connected to changes in astrocyte activities^[23]. Interestingly, aPLs (i.e., aCL) were reported to be frequently immunoreactive and could bind with their target receptors on astrocytes^[24], which show a possible involvement of aPLs in the activation of brain astrocytes and subsequent CNS hyperexcitability in epileptic patients. In addition, aCL have been reported to bind with the cell membrane of the neurons, causing immune complex formation that further induces immune responses resulting in several brain diseases, including epilepsy^[25,26]. Also, it has been hypothesized that cytokines and aPLs can induce the disruption of blood-brain barrier and then exert toxic effects on glial cells and neurons^[27], involved in the development of epilepsy^[28]. Interleukin (IL)-1 β is one of the main cytokines increasing in patients with epilepsy^[29] and is considered a contributing factor to the generation of epilepsy^[30]. Interestingly, induction of IL-1 β has been reported by aPLs in dendritic cells and monocytes^[31].

To the best of our knowledge, this is the first study addressing the correlation between the level of aCL and response to IVIg in children with epilepsy. We found that the high level of aCL in epileptic patients could predict a positive response to IVIg, which can guide treatment selection. This relationship implies that IVIg might be more effective in treating epileptic patients with positive aCL than those with negative aCL. In addition, a positive response to IVIg therapy supports the hypothesis of immune system involvement in this disease. According to the Response to Immunotherapy in Epilepsy (RITE) score scale, neural plasma membrane auto-antibody (CASPR-2 Ab, LGI-1 Ab, mGluR-5, mGluR-2, mGluR-1, DPPX, GABAB-R, AMPA-R Ab, GABAA-R Ab, and NMDA-R Ab) have an essential role in predicting positive response to immunomodulator treatments among epileptic patients^[32]. Our results showed that aCL could be added to this scale. Further prospective randomized studies are needed to investigate this predictive value.

In the present study, patients with a longer duration of epilepsy had more levels of aCL. It was similar to the study of Eriksson *et al.*^[9] that reported more duration of epilepsy in aCL positive

patients compared to aCL negative patients (4.3 versus 2.7 years; p value = 0.064). Similar to the study of Eriksson *et al.*^[9], in our study, there was a significantly higher level of aCL in patients with combined epilepsy than those with other types of epilepsy.

In our study, there was a significant relationship between the value of IgG class aCL and the duration of disease when the sample was taken. It was similar to the study of Bektaş *et al.*^[18] on 80 children with epilepsy which shows that 35% of newly diagnosed patients had at least one positive Ab (aCL/IgG, NMDAR, GAD, paraneoplastic, antithyroid peroxidase, anti-b2-glycoprotein I, and ANA Abs), while it was positive in 55% of non-newly diagnosed patients (p value = 0.072, odds ratio: 1.51, 95% CI: 0.94–2.45).

On neurologic and MRI examination, the majority of our patients (62.5% and 72.5%, respectively) were normal. It was similar to the study of Bektaş *et al.*^[18] that reported normal findings in 82.5% of MRI and 73.8% of neurologic examinations on epileptic children. However, Liimatainen *et al.*^[11] declared that only 36.1% of adults with refractory focal epilepsy had normal MRI.

In our study, patients with a higher frequency of seizures had more titers of aCL compared to others. It was different from the study of Liimatainen *et al.*^[11] that showed there was no relationship between the level of aCL and seizure frequency in the subjects with refractory focal epilepsy. This difference may be caused by the different populations enrolled in studies. Liimatainen *et al.*^[11] studied adult patients with refractory focal epilepsy, but we studied children with different types of epilepsy.

In our study, patients with ESES patterns on EGG had the highest level of aCL, and it was statistically significant. In literature, there were two studies that investigated cytokine profiles of patients with ESES^[33,34], which reported elevated levels of IL-1, IL-6, IL-8, and IL-10 in patients with ESES in comparison with healthy controls. This result proposed the possible involvement of the immune system in the onset and pathogenesis of ESES. Also, it could indicate that immunomodulatory therapy could be helpful in patients with ESES.

The main limitation of this study is the small number of patients. However, the strengths of our study are the homogeneity of cases and controls and

its prospective methodology.

6. Conclusion

The aPLs (aCL/IgG) levels were significantly higher in children with epilepsy than age- and sex-matched healthy controls and patients with appropriate responses to IVIg therapy than those without response. So, screening for aCL may help in the timely diagnosis of epilepsy and initiation of appropriate treatment. A trial of immunomodulator treatments (e.g., IVIg) should be considered in epileptic patients spatially in patients with positive titers of aCL, ESES, and combined epilepsy.

Conflict of interest

The authors declared no conflict of interest.

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