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Prevalence of antiphospholipid and antinuclear antibodies in children with epilepsy

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C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Tamás Constantin[1ABCDEF], Tamás Kálovics[1B], Andrea Ponyi[1ACDE], Eszter Nagy[2B], Krisztina Sallai[2B], Léna Szabó[1BF], Miklós Garami[1AD], Judit Müller[1B], Péter Gergely[2AD], Katalin Dankó[3AD], György Fekete[1ADE], Rozália Kálmánchey[1ABDE]

[1] 2nd Department of Pediatrics, Semmelweis University, Faculty of Medicine, Budapest, Hungary
[2] Central Laboratory of Immunology, Semmelweis University, Budapest, Hungary
[3] 3rd Department of Internal Medicine, Division of Clinical Immunology, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary

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Summary

Background: Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent venous thrombosis or arterial occlusive events and fetal losses associated with elevated levels of antiphospholipid antibodies (aPLs).

Material/Methods: The presence of antinuclear, anti-β2-glycoprotein I, and anticardiolipin antibodies were investigated in 60 consecutive children with epilepsy who were followed up in a single Hungarian center.

Results: Almost 50% (28/60) of the patients were ANA positive. Twelve (20%) patients had moderate titer (1:160) of ANA. Anti-C1q antibody was positive in 4 cases, all of them symptom free considering renal manifestation of lupus. Interestingly, only 1 child had aCL antibody, while 6/43 patients were LAC positive. Five were also ANA positive among the LAC positive patients (4 children with moderate titer). Anti-β2GPI antibody positivity was not detected in this cohort of patients.

Conclusions: The clinical relevance of aPL tests in childhood are difficult to explain. In the present study, obviously lower total prevalence of aPLs (aCL and anti-β2GPI) was observed in children with epilepsy than in previously reported investigations (20–30%). The higher amount of LAC-positive patients indicates that coagulation studies (LAC) should be included in the neuroimmunological assessment of suspected APS patients with epileptic disorders. The difference between the results of serological and LAC studies could be explained by the possible positivity of other, uninvestigated antibodies. The wide spectrum of detected immunological alterations highlight the importance of the participation of pediatric rheumatologists in the management of patients with idiopathic epilepsy or with secondary induced autoimmune disease due to antiepileptic medications.

key words: **antiphospholipid antibodies • lupus anticoagulant • epilepsy**

Abbreviations: **aCL** – anticardiolipin; **ANA** – antinuclear; **anti-β2GPI** – anti-beta-2-glycoprotein I antibodies (a); **APS** – antiphospholipid syndrome; **LAC** – lupus anticoagulant; **SLE** – systemic lupus erythematosus

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Author's address: Tamás Constantin, Unit of Pediatric Immunology, 2nd Department of Pediatrics, Semmelweis University, Tűzoltó u. 7-9, H-1094 Budapest, Hungary, e-mail: ctamas@gyer2.sote.hu

Background

Antiphospholipid syndrome (APS, also called Hughes syndrome) is an autoimmune disorder characterized by recurrent venous thrombosis or arterial occlusive events and fetal losses associated with elevated levels of antiphospholipid antibodies (aPLs). The most common clinical manifestations of APS in childhood are deep venous thrombosis, ischemic stroke syndromes, superior sagittal sinus thrombosis, Budd-Chiari syndrome, and arterial and venous thrombosis of kidney, adrenal glands, lung, and heart [1,2]. Although headache, migraine, epilepsy, and chorea were noted in the first publications, the international Saporo criteria did not consider any neurological features other than ischemic stroke when it is documented on brain magnetic resonance imaging (MRI) [3–11]. Therefore the diagnosis of APS is based on the presence of at least one clinical finding (thromboembolic episode or abortion) and one laboratory criterion (elevated aCL antibodies or lupus anticoagulant detected on at least two occasions more than six weeks apart) [7–10]. To date, many neuropsychiatric manifestations (cerebrovascular diseases, headache/migraine, dementia, epilepsy, cognitive dysfunction, chorea, psychosis, optic neuropathy, transverse myelitis, sensorineural hearing loss) have been described in association with APS [12,13].

Based on the data of recent clinical studies, increased prevalence of aPL antibodies has been suggested in patients with epilepsy, both in adults [14–16] and in children [16–20]. Increased frequency of antinuclear antibodies (ANAs) has also been reported in patients with epilepsy [14,15] (Tables 1,2.). Although antiepileptic medications (phenytoin, carbamazepine, valproate) have been known to cause drug-induced lupus syndromes and to trigger exacerbations of SLE, these studies have not revealed any association between the presence of autoantibodies and antiepileptic medications [14,15,20]. It has to be also mentioned that neuroimaging studies of the brain found no ischemic lesions in aCL-positive patients with epilepsy [14]. The pathological role of these antibodies in patients with epilepsy remains unclear [16,21–23]. The two main pathogenic mechanisms are thrombotic events in the central nervous system (CNS) and direct immune-mediated cellular damage. In experimental studies, Chapman et al. described aPL-mediated disruption of neuronal function by direct action on nerve terminals. Their study group also demonstrated functional CNS involvement in experimental models of APS [24–27]. Successful immunomodulatory treatment in some cases of intractable childhood epilepsies also suggests that immune mechanisms are involved in the pathogenesis.

Material and Methods

Patient selection

Sixty consecutive in- and out-patients with epilepsy who were diagnosed, treated, and followed up by the 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary, were identified. The diagnosis of epilepsy was made between 1987 and 2004. We analyzed the medical records retrospectively, recording the following data: age, sex, the time of diagnosis, time of follow-up, type and duration of epilepsy, frequency of seizures, time from the last seizure, results of neuroimaging and EEG data, antiepileptic medication administered during the disease course, and the significant previous history. All patients were Caucasian. Missing values among the investigated factors in the dataset were noted in each case. Patients with acute or chronic infection were excluded from this study. Data collection was terminated by January 1, 2007, when the present study was performed. Duration of follow-up was determined from time 0, corresponding to the date of diagnosis, to the date of obtaining blood for laboratory analysis.

Diagnosis

The Neurology Unit at the 2nd Department of Pediatrics is a tertiary referral center seeing and consulting patients with epilepsy from the whole country and from neighboring Central European countries. A pediatric neurologist with academic experience in the field of epileptology (KR) performed the clinical and neurological examinations in all cases. Evaluation of clinical signs and symptoms of immune system disorders (especially for autoimmune diseases) was performed at the Rheumatology Unit at the 2nd Department of Pediatrics (CT, PA). Physical examination of the musculoskeletal system, 24-hour blood-pressure monitoring, and urine analysis were performed in suspected cases. Blood counts were analyzed to exclude cytopenias (GM, JM).

Classification of epilepsy

Epilepsy was diagnosed by clinical history and electroencephalographic recording. The type of epilepsy was determined according to the International Classification of Epilepsies and Epileptic syndromes (Commission, 1989) based on the characteristic of seizure and EEG data (including video EEG monitoring in all cases) [28,29]. The patients were classified into the five main categories of epilepsy:

1. Localization-related idiopathic epilepsy (e.g. benign childhood epilepsy with centrotemporal spikes) or cryptogenic epilepsy (with normal brain MRI and neurodevelopment).
2. Localization-related symptomatic epilepsy.
3. Generalized idiopathic epilepsy (e.g. childhood absence epilepsy).
4. Generalized symptomatic or cryptogenic epilepsy (e.g. infantile spasms-West syndrome, Lennox-Gastaut syndrome).
5. Undetermined whether focal or generalized epilepsy.

The diagnosis of Landau-Kleffner syndrome was assigned if the child had regression of language in association with seizure disorder with minimal or no disruption of social skills [30,31].

Laboratory analysis

According to the wide spectrum of published immunological alterations among patients with epilepsy, all children underwent a standardized evaluation of their immune status at our Institute. Antibodies were assessed during routine follow-up. All tests were performed at the Central Laboratory of Immunology, Semmelweis University (GP, NE, SK). Serum levels of IgA, IgG, and IgM were determined by turbidimetric measurements (Randox, Ireland). Levels of the complement components C3 and C4 were quantitatively determined by turbidimetric measurements (Randox, Ireland). Results were analyzed according to the age-specific normal values.

Table 1. aPL antibodies in adults, adolescents and children with epilepsy [14,15,20,36].

aPL antibodies in adult patients with epilepsy	
Peltola et al.: prevalence of IgG aCL	
Newly diagnosed patients (n=50):	21%
Localization-related epilepsy (n=50):	14%
Generalized epilepsy (n=52):	8%
Controls (n=83):	7%
Verrot et al.: prevalence of IgG aCL	
41/163 patients:	25%
Remarks:	
No association between Abs and medications.	
Imaging of the brain found no ischaemic lesion in the aCL positive group.	
aPL antibodies in young patients with epilepsy (Cimaz et al.)	
n=142 (median age: 10ys, range: 1–25 ys)	
Prevalence of aCL:	10.6%
IgM aCL:	1.4%
IgG aCL:	7.7%
IgM+IgG aCL:	1.4%
Prevalence of anti-β2GPI:	17.6%
IgM anti-β2GPI:	2.8%
IgG anti-β2GPI:	12%
IgM+IgG anti-β2GPI:	2.8%
aPL antibodies in children with epilepsy (Eriksson et al.)	
In study group (n=50)	
Prevalence of IgG aCL:	44%
Prevalence of IgG anti-β2GPI:	10%
Prevalence of ANA:	16%
Control group (n=20)	
Prevalence of IgG aCL:	10%
Prevalence of IgG anti-β2GPI:	0%
Prevalence of ANA:	0%

Anticardiolipin and anti-β2GPI autoantibodies were measured by commercial enzyme immunoassays (Orgentec Inc., Germany). All samples were screened for aCLs (IgG/A/M) and anti-β2-glycoprotein I (aβ2GPI, IgG/A/M). For both screening tests the cut-off values were 10 U/ml (range: 0–90 U/ml). Positive samples were further typed for aCL Ig class (IgG and IgM). For aCL IgG, samples with values between 10–20 GPLU/ml were considered as low positive, 20–60 GPLU/ml as moderately positive, and above 60 GPLU/ml as strongly positive. ANAs were detected by a standard indirect immunofluorescence method using Hep-2 cells as antigens (Binding Site, UK). Sera were tested in 40-fold and 160-fold dilutions along with appropriate controls. FITC (flouresce-in-isothiocyonate)-labeled polyclonal rabbit anti-human IgG (Dako, Denmark) was used as the conjugate. Any nuclear staining detected by fluorescent microscopy was reported as a positive result. Anti-C1q antibodies were detected by an in-house ELISA. Purified human C1q (Sigma, USA) in sodium-carbonate buffer was used as coat, rabbit anti-human IgG labeled with horseradish-peroxidase (Dako, Denmark) was used as conjugate, and OPD (ortophenyl-diamine) with hydrogen-peroxide was used as substrate. According to the optical density (OD) measured in the wells at 492/620 nm, samples were considered negative, weakly positive, or positive. The cut-off OD was calculated on the basis of the data of 100 healthy individuals and was set at mean OD + 2 SD. Three independent tests were used to screen for the presence of LAC: diluted prothrombin time (1:200, Innovin; Dade Behring, USA), lupus-sensitive aPTT (Diagnostica Stago, France), and diluted Russell's viper venom time (Life Diagnostics, Australia). In case of prolonged clotting times, LAC positivity was confirmed by phospholipid neutralization.

Table 2. ANA positivity among patients with epilepsy [14,15,20,36].

Eriksson et al.	
Children with epilepsy:	8/50 (16%)
Controls:	0/0
Cimaz et al.	
Young patients with epilepsy:	10/142 (7%)
Verrot et al.	
Adult patients:	41/163 (25%)
Controls:	10/100 (10%)
Peltola et al. (adult patients)	
Localization-related epilepsy:	12/50 (24%)
Newly diagnosed seizures:	11/52 (21%)
Generalized:	4/50 (8%)
Controls:	10/83 (12%)

Neuroimaging studies

Before the neuroimmunological assessment, brain computed tomography or MRI scans were performed in most (52/60, 87%) patients during the disease course [32]. None of them had ischemic lesions, but further analyses were not carried out as part of the present study.

Results

Demographic data and clinical characteristics of the patients

The mean age at the time of diagnosis was 6.2 years (range: 1–17 years). The male: female ratio was 1:0.67. The mean duration of the disease was 4.8 years. The distribution of

Table 3. Distribution of our patients according to the type of epilepsy.

Type of epilepsy	n=60	ANA 1:40	ANA 1:160	LAC
1. Localization-related idiopathic/cryptogenic:	8 (13%)	2/8 (25%)	1/8 (12%)	1/8 (12%)
2. Localization-related symptomatic:	13 (22%)	6/13 (46%)	3/13 (23%)	3/7 (43%)
3. Generalized idiopathic:	28 (47%)	16/28 (57%)	6/28 (21%)	0/21
4. Generalized symptomatic/cryptogenic:	1 (1%)	0/1	0/1	0/1
5. Undetermined:	7 (12%)	3/7 (43%)	2/7 (28%)	2/5 (40%)
6. Unclassified:	3 (5%)	1/3 (33%)	0/3	0/1

the patients according to the type of epilepsy is shown in Table 3. Most children were in the group of patients with generalized idiopathic epilepsy. In the view of the seizure frequency, most of the patients achieved good disease control and had only 0–2 attack(s) per year. The mean time between the last episode of seizure and the laboratory analysis was 1.9 years.

Serum level of immunoglobulins

Partial immunglobulin A deficiency was detected in 14/60 (23%) patients. The serum levels of the other immunglobulin subclasses (IgG and IgM) were within the normal range.

Serum level of complements

Mild hypocomplementemia was detected in four children (6%). One of them showed concurrent ANA and LAC positivity with hypocomplementemia (C3, C4). His last seizure was one year before, after which he was symptom-free and no other organ manifestation of lupus was observed. Although the diagnostic criteria for SLE was not fulfilled, the patient was observed for the possible development of systemic disease.

ANA

Twenty-eight of the 60 patients (47%) were ANA positive. Twelve (20%) had moderate titers (1:160) of ANA. Among these patients, anti-C1q antibody was positive in 2 cases, both of which were symptom-free with regard to renal manifestation of lupus.

Anti-C1q antibodies

Four of 60 (6%) patients were anti-C1q antibody positive. Two of them were ANA positive, but none were aDNA positive. Organ manifestations of lupus (renal, articular, or hematological) were not observed.

aCL and LAC

Interestingly, only 1 child (1.5%) had aCL antibody, while 6/43 (14%) patients were LAC positive. Five of the 6 LAC-positive patients were ANA positive as well (4 children with moderate titers). Anti-β2-glycoprotein I antibody positivity was not detected in this cohort of patients.

LAC positivity according to the type of epilepsy

Most of the patients with LAC positivity were classified into the group of localization-related symptomatic (ILEA 2) or undetermined (ILEA 5) epilepsy. Almost 50% of the children had generalized idiopathic epilepsy with no LAC (Table 3). Only 1 patient with aCL antibody was not LAC positive and this child was in the group of generalized idiopathic epilepsy.

Patients with Landau-Kleffner syndrome

Disease of 4 of the patients was classified in the group of Landau-Kleffner syndrome. Sera of 2 children showed ANA positivity (1 in moderate and 1 in high titer). The patient with high-titer ANA positivity has also anti-C1q antibody. While 2 children were LAC positive, aCL antibodies were not detected in this cohort of patients.

Summary of results of possible autoimmune disease

Although no patient with SLE was recognized, many lupus-related immunological alterations (ANA, hypocomplementemia, C1q antibody, aCL-LAC) were observed and one child with possible autoimmune disease and 7 children with possible neuropsychiatric primary APS were identified. Predictive antibodies for renal involvement (lupus nephritis) were detected in 2 children. These patients were observed for the possible development of autoimmune disease.

Discussion

Partial immunoglobulin deficiency has been detected in 20% of patients, as previously described [33–35]. Almost 50% of our patients were ANA positive; in 12 cases of the 28 ANA-positive children the results showed moderate titers. Considering the titer of ANA, lower rates of total (moderate and high) ANA positivity were reported in the available relevant literature [14,15,20,36]. This difference may be caused by the smaller number of patients in this study; therefore further measurements are needed to clarify the validity of this observation. It has to be mentioned that these autoantibodies may occur with different frequencies in the general population as well. Based on the available studies, the prevalence of ANA is 4–22% (depending on the titer of ANA; the prevalence of a moderate titer of ANA in the healthy population is less than 5%) and the prevalence of aCL is 2–14% [37–43].

Table 4. Rate of aPL positivity according to the type of epilepsy [14,20,36].

	Localized idiopath/crypt.	Localized symptomatic	Generalized idiopathic	Generalized sympt/crypt.
Eriksson et al.	n=16	n=9	n=13	n=7
aCL IgG	2 (13%)	2 (22%)	2 (15%)	5 (71%)
anti-β2GPI	0	0	1 (8%)	1 (14%)
Verrot et al.	n=31	n=49	n=34	n=27
aCL IgG	5 (16%)	9 (29%)	5 (16%)	5 (18%)
		Symptomatic	**Cryptogenic**	**Idiopathic**
Cimaz et al.	n=41	19 (46%)	13 (32%)	9 (22%)

Autoantibodies against C1q are best described in adult and childhood patients with systemic lupus erythematosus, where a strong correlation between the occurrence of anti-C1q and severe lupus nephritis (LN) has been observed [44–46]. The unexpected number (6%) of anti-C1q-positive patients in our cohort may indicate a new correlation between these antibodies and other (non-lupus) autoimmune diseases. This hypothesis could be supported by the fact that plasma samples from myasthenia gravis patients also contain anti-C1q antibodies [47]. Until the verification of the possible pathogenic role of these antibodies in epilepsy with experimental models, our observation also could be clarified with the possible development of SLE in these children.

According to data of the relevant literature, a relationship between epilepsy and aCL antibodies is suggested [13,48]. aCL positivity was found in 19% of adult patients with epilepsy by Verrot et al. and approximately 20% of aCL-positive patients had anti-β2GPI autoantibody dependence. None of the patients had a past history of deep venous or arterial thrombosis and the presence of antibodies was not statistically dependent on the type of antiepileptic drug used [14]. Compared with controls, newly diagnosed patients had a significantly greater prevalence of IgG aCL antibodies (10% vs. 7%); the prevalence was 14% in patients with localization-related epilepsy and 8% in patients with generalized epilepsy in a previous study by Peltola et al. The prevalence of IgM aCL antibodies was significantly greater in all seizure groups compared with controls [15]. An overall positivity of 28.8% was detected by Cimaz et al. All types of epilepsy were represented in the positive group. Diffuse ischemic lesions on CT/MRI scans were present in higher percentages in patients who were antibody positive [36].

In the present study, an obviously lower total prevalence of aPLs (aCL and anti-β2GPI) was observed in the children with epilepsy than in the previously reported investigations. Lupus anticoagulant was positive in 6 of 43 cases (14%), while anti-phospholipid antibodies were detected in only 1 child. If we review the relevant papers it seems that the highest frequencies of aCL-positive subjects were found among patients with symptomatic or cryptogenic epilepsies [14,15,20,36] (Table 4). Although the overall frequency of antibodies was the same in both groups of patients and reference subjects in a large population-based cross-sectional study, long duration of epilepsy and suboptimal seizure control were associated with an increased presence of aCLs [49]. Peltola et al. also found an association between aCL positivity and the (larger) number of previous seizures [15]. In our study, most of the children achieved good seizure control even though the mean duration of epilepsy was relatively long. The time between the last seizure and the laboratory analysis was relatively long, the mean time being 24 months, and the mean seizure frequency was also low.

Most of the patients had generalized idiopathic epilepsy, while in previous studies, different types of epilepsies were more equally represented (Tables 3,4). Peltola et al. found that the prevalence of aCL antibodies was greater in patients with localization-related epilepsies than those with generalized epilepsies [15].

Conclusions

The presence of aCL antibodies may reflect the effect of seizures on the immune system. Recent seizures have been associated with autoantibodies and seizures are known to activate cytokine production [27,49–53]. Long duration of epilepsy and suboptimal seizure control are usually found among patients with symptomatic or cryptogenic generalized epilepsies and with undetermined epilepsies in previous studies. On the other hand, our results show that patients with benign epilepsy and good seizure control have the lowest risk of developing aCL antibodies.

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