Features Associated with Epilepsy in the Antiphospholipid Syndrome

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ABSTRACT. ***Objective.*** To assess the frequency of epilepsy in primary and secondary antiphospholipid syndrome (APS); to analyze the clinical and laboratory features characterizing those with epilepsy in a cohort of 538 patients with APS; and to find associated features that would suggest risk factors for epilepsy in APS.

Methods. We analyzed the clinical features of patients with APS who had epilepsy and compared them to the clinical features of non-epileptic APS patients.

Results. Of 538 APS patients, 46 (8.6%) had epilepsy. Epilepsy was more prevalent among APS secondary to systemic lupus erythematosus (SLE) compared to primary APS (13.7% vs 6%; $p < 0.05$). The patients with epilepsy had a higher prevalence of central nervous system (CNS) manifestations including focal ischemic events (strokes or transient ischemic events, 54.3% vs 24.6%; $p < 0.0001$) and amaurosis fugax (15.2% vs 4.9%; $p < 0.05$). APS patients with epilepsy had a higher frequency of valvular pathology (30.4% vs 14.6%; $p < 0.01$), thrombocytopenia (43.5% vs 25%; $p < 0.05$), and livedo reticularis (26.1% vs 11.5%; $p < 0.01$). The multivariate logistic regression analysis found CNS thromboembolic events as the most significant factor associated with epilepsy, with an odds ratio (OR) of 4.05 (95% confidence interval, CI: 2.05–8), followed by SLE (OR 1.4, 95% CI 1.2–4.7), and valvular vegetations (OR 2.87, 95% CI 1–8.27).

Conclusion. Epilepsy is common in APS and most of the risk seems to be linked to vascular disease as manifested by extensive CNS involvement, valvulopathy, and livedo reticularis and to the presence of SLE. These factors, however, explain only part of the increased occurrence of epilepsy in APS and other causes such as direct immune interaction in the brain should be investigated. (J Rheumatol 2004;31:1344–8)

Key Indexing Terms:

EPILEPSY ANTIPHOSPHOLIPID SYNDROME VALVULAR HEART DISEASE
THROMBOCYTOPENIA LIVEDO RETICULARIS ANTIPHOSPHOLIPID ANTIBODIES

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Part of the Euro APS Study.

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Submitted November 8, 2002; revision accepted January 14, 2004.

The antiphospholipid syndrome (APS) is characterized by venous or arterial thromboses and/or obstetric complications, accompanied by an increased level of antiphospholipid antibodies (aPL)[1-3]. In about half of the patients, the syndrome is classified as primary[4] (in the absence of an underlying disorder), whereas in the rest it is secondary, mainly to systemic lupus erythematosus (SLE)[3].

A large spectrum of clinical manifestations has been repeatedly reported to be related to APS, encompassing cardiac disorders (mainly valvular thickening and vegetations)[5], skin disorders (i.e., livedo reticularis), and neurological disorders (cerebral infarcts, migraine, epilepsy, chorea)[6,7]. Cerebral infarcts are the most commonly described. Epilepsy has been reported in APS patients but its epidemiology, related clinical phenomena, and pathogenesis are still unclear. Most published data regarding epilepsy are related to SLE or to APS secondary to SLE (APS/SLE), with limited data regarding epilepsy in primary APS. In a study of 221 SLE patients, 21 patients had epilepsy; however, only 9 of them presented classic features of APS[8]. Seizures were reported in 8 out of 39 patients with SLE who were also positive for IgG anticardiolipin (aCL)[9]. In a 10-year followup of 39 APS patients, 3 patients developed seizures[10]. A high prevalence of aCL and anti-$ß_2$ glycoprotein I antibodies (anti-$ß_2$-GPI) was reported in patients with epilepsy[11]. Epilepsy was reported in a recent cohort study of 1000 APS patients in 3.4% of the patients at the onset of their disease and in 7% of the patients at time of the study[12].

We assessed the frequency of epilepsy in primary and secondary APS, and investigated the associated clinical and laboratory features that may suggest risk factors and causes of epilepsy in patients with APS.

MATERIALS AND METHODS

Selection of patients. Clinical data were collected in a collaborative multinational, multicenter project involving centers in the Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, The Netherlands, Portugal, Slovenia, Spain, Sweden, and the United Kingdom. Investigators in all participating centers were experienced in the management of patients with APS. Data collection was standardized as described[12]. The patients were collected in a random fashion without bias for epilepsy. There is no overlap with the 1000 patients described in a previous publication[12]. The study was performed according to the principles of the Declaration of Helsinki.

Definition of clinical features. The participating physicians were instructed to include patients with the diagnosis of APS[13]. This included patients who had one or more clinical episodes of arterial, venous, or small vessel thrombosis and/or typical obstetric complications with lupus anticoagulant or aCL (IgG and/or IgM isotype) in their blood, in medium or high titer on 2 or more occasions. Participating centers were asked to specify if patients fulfilled the American College of Rheumatology criteria for SLE[14].

Epilepsy was defined by standard clinical criteria of at least 2 separate episodes of unprovoked seizures with an interval greater than 24 h. Seizures could be either simple partial, complex partial, or secondarily generalized tonic-clonic, and had to be unrelated to metabolic abnormalities or to drug or medication use or withdrawal, and without other provoking factors such as hypoxia or cerebral hypoperfusion. Acute symptomatic seizures were not included.

Medical histories were documented, and the patients underwent a medical interview and a general physical examination by an internist or a rheumatologist. Serum samples were collected for immunological testing, as outlined[12].

All patients underwent echocardiography, and 103 had transesophageal echocardiograms.

Statistical analysis. The intergroup analysis of the different variables between the epileptic group and the non-epileptic group was carried out using a chi-squared or Fisher's exact test for categorical variables and a t test for continuous variables. Statistical significance was indicated by a 2-tailed p value of less than 0.05. Because of the many variables examined, a logistic regression analysis was performed for the multivariate analysis.

RESULTS

The study included 538 patients, 87.8% (472) female and 12.2% (66) male, with a female/male ratio of 7.15:1. The mean age at onset of APS was 31.2 ± 10.5 (range 9–73, median 29). The mean age was 38.6 ± 11.4 years (range 14–75, median 36). Fifty-three percent of the patients had primary APS, 35% had APS associated with SLE, and 12%

Table 1. Clinical and demographic characteristics of APS patients with and without epilepsy.

Variable	With Epilepsy, n = 46	No Epilepsy, n = 492
Age at onset of APS, yrs (mean ± SD)*	26.5 ± 10.4	31.7 ± 10.4
Age at study entry, yrs (mean ± SD)	36.3 ± 9.9	38.8 ± 11.5
Male, %	17.4	10.9
Female, %	82.6	89.1
Ratio	1/5	1/8
Primary APS, %	34.8	55.5
APS secondary to SLE*, %	50	32.1
APS secondary to other autoimmune diseases, %	15.2	12.4

* $p < 0.05$.

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had APS associated with other autoimmune diseases (lupus-like syndrome, Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis).

The group of patients with epilepsy included 46 patients (8.6%), 38 females and 8 males (Table 1). The mean age at onset was 26.5 ± 10.4 years, significantly younger than the non-epileptics (31.7 ± 10.4; $p < 0.05$). Sixteen epileptic patients had primary APS (35%), 23/46 (50%) had SLE, and 7 (15.2%) patients had APS secondary to other autoimmune diseases. SLE patients had a higher risk than patients with primary APS for developing epilepsy (13.7% vs 6%; $p < 0.05$).

The frequencies of common clinical manifestations of APS in the epileptic patients as compared to the non-epileptic patients are shown in Table 2. The presence of central nervous system (CNS) manifestations was significantly more frequent in the epileptic APS patients, and this difference was specifically due to CNS thromboembolic events.

The epileptic APS patients had more frequent valvular dysfunction and valvular vegetations compared to non-epileptic APS patients (overall valvular involvement: 30.4% vs 14.6%; $p < 0.01$; Table 2). The occurrences of thrombocytopenia, livedo reticularis, and autoimmune hemolytic anemia were also significantly higher among the epileptic APS patients compared to those without epilepsy (Table 2). Fetal loss was significantly higher among non-epileptics. The multivariate logistic regression analysis found CNS thromboembolic events as the most significant factor associated with epilepsy with an odds ratio (OR) of 4.05 (95% confidence interval, CI: 2.05–8), followed by SLE (OR 1.4, 95% CI 1.2–4.7), and valvular vegetations (OR 2.87, 95% CI 1–8.27).

Table 2. Clinical APS manifestations in APS patients with and without epilepsy. Results are given as percentages. Total CNS manifestations included TIA, chorea, stroke, migraine, and amaurosis fugax. Cardiac manifestations included valvular dysfunction or vegetations, and acute ischemic events. Valvular dysfunction was defined as mitral or aortic valve regurgitation or stenosis. Cutaneous manifestations included livedo reticularis, ulcers, pseudovasculitic lesions, digital ischemia, splinters, and melanoderma. Obstetric complications included fetal loss (late or early), preeclampsia or ecclampsia, and chorea gravidarum.

Variable	Epileptic (n = 46)	Non-Epileptic (n = 492)	p
Total CNS manifestations	69.6	41.2	< 0.01
Stroke or TIA	54.3	24.6	< 0.0001
Chorea	4.3	0.9	NS
Migraine	21.7	13.5	NS
Amaurosis fugax	15.2	4.9	< 0.05
Total cardiac manifestations	43.5	22.3	< 0.01
Valvular involvement	30.4	14.6	< 0.01
Valvular dysfunction	23.9	11.7	< 0.01
Valvular vegetations	17.4	4.6	< 0.01
Pseudoendocarditis	8.7	1.1	< 0.01
Total hematological manifestations	52.2	31	< 0.01
Thrombocytopenia	43.5	25	< 0.05
Autoimmune hemolytic anemia	17.4	8.2	0.053
Total cutaneous manifestations	43.5	22.1	< 0.01
Livedo reticularis	26.1	11.5	< 0.01
Renal involvement (thrombotic)	28.3	9.5	< 0.001
Total obstetric manifestations	42.1	52.6	NS
Fetal loss	19.6	38.5	< 0.05

TIA: transient ischemic attack, NS: not significant.

DISCUSSION

In this population of patients with primary and secondary APS, the prevalence of epilepsy was 8.6%. This is clearly higher than the 0.5–1% expected in the general population and is in broad agreement with previous descriptions of epilepsy and APS[8-11]. It is not clear, however, what the pathogenesis of epilepsy is in these cases, since possible explanations include focal brain ischemic lesions, systemic autoimmune disease such as SLE, and direct effects of aPL on the brain. As discussed below, the large number of patients in the present study allowed some insight into these questions.

While the association of SLE with epilepsy is well established, less sound evidence exists regarding the frequency of epilepsy in primary APS[15]. Indeed, in our study, the frequency of epilepsy in the primary APS patients was 6%, significantly lower than in the APS/SLE patients (13%; $p < 0.01$). SLE may cause epilepsy by a number of APS-independent mechanisms including vasculitis, metabolic disorders, and cerebritis, which may explain such a difference. Such an assumption would be compatible with previous studies that have shown a high prevalence of epilepsy in SLE patients in the absence of APS. On the other hand, the large number of patients with epilepsy and primary APS in our study argue for a direct association of APS with epilepsy.

The highly significant association of epilepsy with stroke in the APS patients suggests that this is a key mechanism in the pathogenesis of epileptic foci in these patients. This is compatible with previous neuroimaging findings showing small foci of abnormal signal in the subcortical white matter in APS patients who experienced seizures. It is important to note, however, that in a significant number of epileptic APS patients, no detectable infarct can be found by conventional imaging techniques[16]. Positron emission tomography (PET) studies in APS patients with CNS manifestations may help to clarify this puzzling phenomenon, by showing decreased glucose metabolism in the perivascular areas, suggesting a subtle ischemic insult[17]. Further, a pathological examination in a young APS patient who had complex partial seizures and transient ischemic events showed widespread small cerebral arterial thrombi causing extensive microinfarcts within the cerebral cortex[18]. This mechanism is supported

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by observations performed in patients with Sneddon's syndrome (ischemic cerebral events and livedo reticularis). Among 46 patients with Sneddon's syndrome and no criteria for SLE, seizures were present in 36.8% of the patients with aPL versus 11.1% of those without aPL ($p < 0.05$), whereas both groups had otherwise similar clinical and imaging neurological manifestations. Interestingly, thrombocytopenia was also associated with the presence of aPL[19], as it is in this study, implying perhaps an immune-coagulation interaction. The increased occurrence of valvular thickening and vegetations in our patients strongly supports a cardioembolic mechanism for stroke from valvular lesions usually consisting of fibrin deposits[5]. The development of valve pathology is probably mediated by immunological injury, as shown by Ziporen, *et al*[20] and Afek, *et al*[21], who have shown an interaction of aPL antibodies with damaged valves.

A key issue is whether stroke is the exclusive cause of epilepsy in patients with primary APS. Our findings provide a number of arguments against such a generalization: The prevalence of post-stroke epilepsy is well established to be in the range of 10%[22]. It is reasonable to assume that this would tend to be lower in APS patients with largely subcortical ischemic strokes, in contrast to unselected populations of patients including large numbers of cortical strokes and hemorrhages. Contrary to this expectation, the prevalence of post-stroke epilepsy was 17% in APS patients in our study, suggesting involvement of additional factors.

The association between epilepsy and APS had long been suspected and has been supported by the finding of high titers of autoantibodies, including aPL, in epileptic patients. Anti-CNS antibodies have lately been found in frontal cortex immunoblots, but not in cerebellar immunoblots, in children with epilepsy[23]. The specific nature of these antibodies is unknown, but other investigators have reported autoantibodies to glutamic acid decarboxylase in epilepsy patients[24,25], as well as aPL[26,27]. A recent study performed on epilepsy patients found aCL in 19%, mainly IgG, in the absence of thrombotic episodes[26]. Another study found aCL in 43% of epilepsy patients, mainly IgM[28]. The presence of aCL did not depend on the antiepileptic drugs used. Patients with newly diagnosed epilepsy who were not medicated were also found to have aPL (mainly anti-$ß_2$-GPI)[29]. In a recent study, 44% of children with epilepsy had aCL compared with only 10% of healthy controls; 10% of the children with epilepsy were positive for IgG anti-$ß_2$-GPI, compared to none of the healthy controls[30]. Direct support for a causative role of aPL in epilepsy comes from studies showing that IgG aPL can directly permeabilize and depolarize brain synaptoneurosomes[31].

In conclusion, epilepsy is associated with APS and this is explained to a large degree, but not exclusively, by association with SLE and with stroke. Management of APS patients with epilepsy should take into account these factors as well as the possibility of a direct role of aPL in epilepsy.

Our study has several limitations: Brain imaging data that may provide more insight into the origin of the epileptogenic foci were not collected; the seizure history was limited and does not enable us to better characterize the epilepsy in this patient population in terms of seizure types, localization of seizure foci, temporal relationship between the onset of epilepsy and previous strokes, and response to antiepilepsy drugs and to treatment of APS. CNS thromboembolic events were clinically diagnosed in this study, so that there is a possibility that some events assumed to be thromboembolic on clinical grounds may in fact not have been thromboembolic. In order to address these questions we are now undertaking a prospective study integrating clinical, immunological, electroencephalogram, and neuroimaging data.

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