HEADACHE, ANTIPHOSPHOLIPID ANTIBODIES AND CEREBRAL ISCHEMIA IN PATIENTS WITH SYSTEMIC IMMUNE-MEDIATED DISEASES

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ABSTRACT

The antiphospholipid syndrome (APS) is defined by the constant presence of antiphospholipid antibodies (aPL), together with diverse systemic clinical manifestations such as thrombosis, and recurrent spontaneous abortions. By the actual classification criteria, the only neurological manifestation diagnostic of APS is ischemic stroke. However, other neurological manifestations have been repeatedly reported in case studies of APS patients. Among these manifestations, headache and especially migraine was commonly reported in APS patients and is one of the classical features described by Hughes as related to aPL. However, controversies were raised by studies who failed to confirm this association.

We studied the association between aPL and headache syndromes in a retrospective manner in 428 patients with inflammatory connective tissue diseases.

We found that migraine alone, not headache all types, is significantly associated with aPL in patients with systemic immune disease. The presence of cerebral ischemia was also studied in patients with headache and aPL. In SLE patients, headache (all types) is significantly associated with positive titers of aPL, and cerebral ischemic lesions are significantly encountered.

Even that the association migraine – aPL can be explained also by their separate high frequency in patients with immune systemic disease, the association of ischemic lesions in these patients suggest the need to define a sub-group at risk, for whom headache can be a marker and anticoagulants can be discussed.

The antiphospholipid syndrome (APS) is defined by the presence of laboratory markers for antiphospholipid antibodies (aPL), demonstrated by ELISA's for antibodies against phospholipids and associated phospholipids-binding cofactor proteins and/or circulating lupus anticoagulant (LA) together with diverse systemic clinical manifestations such as thrombosis, and recurrent spontaneous abortions. By criteria set out in Sapporo, the only neurological manifestation diagnostic of APS is ischemic stroke (1).

Although other neurological manifestations have been repeatedly reported in case studies of APS patients, the authors of the Sapporo criteria did not consider transient cerebral ischemia, transverse myelopathy multiple-sclerosis-like syndrome, chorea and migraine sufficiently strongly associated with APS to warrant their inclusion as diagnostic criteria (2).

Among these manifestations, headache and especially migraine was commonly reported in APS patients and is one of the classical features described by Hughes as related to aPL. However, controversies were raised by studies who failed to confirm this association. The importance of the subject is emphasized by the great number of patients with migraine that are usually seen in the setting of a neurological department, but also by the high frequency of headache among patients with inflammatory connective tissue diseases who can also associate aPL.

One can study the association headache – aPL in two manners. Firstly, to search for the aPL immunoreactivity in patients with migraine, ideal in a prospective way.

This follow-up study implies some difficulty in a practical setting since headache is a non-specific syndrome, there is lack of specific association between headache and various diseases and a study for each association is necessary.

Secondly, to search for the presence of headache in patients with medical conditions known to associate aPL more frequently. In this spirit, we studied the association between aPL and headache syndromes in a retrospective manner in 428 patients with inflammatory connective tissue diseases.

METHODS

428 patients with connective tissue diseases admitted in the departments of Neurology (1998-2001) and Internal Medicine (2000-2001) of Colentina Hospital were studied. The inclusion criteria were:

1. diagnostic according to current criteria of connective tissue disease, systemic/isolated cerebral vasculitis, primary or secondary APS;
2. at least one assay for aPL.

The aim of the study was to determine if there is any correlation between aPL immunoreactivity and headache, especially migraine. This implied the identification of patients with non-stroke headache syndrome and aPL immunoreactivity, the attempt to establish any correlation between aPL and headache and also between aPL and ischemia in these patients.

MEASUREMENT OF ANTIBODIES

Anticardioplipin antibodies (aCL) and Lupus Anticoagulat (LA) were the aPL subtypes determined in the study.

Determination of aCL antibodies was performed by standardized ELISA for IgG isotype (BIO-RAD) with bovine calf serum in the sample diluent as the source of $ß_2$GPI.) Blood was drawn from patients without anticoagulants and centrifuged for 10 minutes at 1600 rpm. Serum was stored at minus 80°C and thawed at room temperature immediately before performing the assay. The antigen (bovine heart cardiolipin) was diluted in ethanol (45 µg/ml). 30 µg of this solution was applied to the first four rows of ELISA plate wells (96 wells, in 8 rows and 12 columns). Antigen was not added to the first column, which remained „blank". Another four rows were coated with ethanol without the antigen to establish nonspecific bounding values. These values were subtracted from the anticardiolipin coated plates to give specificity to the method. The plates were allowed to dry overnight. 100 µl of phosphate buffered saline was added to the wells on the next day, except for the "blank" column. After one minute, the phosphate-buffered saline was poured out and the plate was beaten out over a paper towel until dry. 200 µl of phosphate buffered saline with 10% fetal calf serum was added to all wells as a blocking buffer and incubated for 1.5 hours. The blocking buffer reagent was then poured out from the plates, which were once again beaten out over a paper towel until dry. This last step was repeated once more with a one minute incubation of phosphate-buffered saline. 50 µl of the patients' serum was added to all wells, except for the „blank" one and dried at room temperature for two hours. The plates were washed three times with 200µl of phosphate buffered saline. The plates were dried and 50µl of indirect antibody conjugated reagent was added to the wells, except for the blank column. Rows one to four received conjugated IgM and rows five to eight received conjugated IgG. After one hour of incubation at room temperature, the plates were washed with 200 µl of phosphate-buffered saline and beaten out to dry. 50 µl of diethanolamine substrate was added to all wells and incubated at 37°C in the dark. The reaction was stopped by the addition of 50 µl of NaOH 3M. The optical density was determined at 405 nm in a Tibertek densitometer. The conversion was done using standars of Phospholipid Standardization Laboratory, Louisville.

Results are expressed as GPL units for the IgG (positive 23 GPL) aCL antibodies, with 1 unit being equivalent to 1 µg/mL of an affinity-purified standard IgG aCL antibody sample. All tests met the quality control standards as determined by the manufacturer.

Lupus anticoagulant was detected using Russel-venom time, as previously described (3).

First stage: prolonging of clotting in at least one in vitro phospholipid-dependent clotting test with the use of platelet-poor plasma. Tests can be subdivided according to coagulation cascad. Extrinsic pathway (diluted prothrombin time), intrinsic pathway (aPTT, diluted aPTT, silica-coloidal clotting time and kaolin clotting time), common on final pathway (dilute Russel's viper venom time).

Second stage: failure in correcting prolonged clotting time by mixing normal patient plasma.

Third stage: confirmation of presence of lupic anticoagulant antibody by shortening or correction of prolonging of clotting time after the addition of excess phospholipids or platelets.

Fourth stage: exclusion of coagulopathies by using assays for specific factors if confirming tests are negative or if a specific factor is suspected.

STATISTICAL ANALYSIS

Continuous variables have been analyzed using Pearson's chi square test. When a studied group was less than five, Yates's test was utilized. Two-tailed Fischer's exact test was utilized for unvaried analysis. Odd ratios for specific associations were calculated and confidence. Intervals were estimated using Woolf's approximation. The level of statistical significance was fixed at 0,05. Software for statistic analysis was utilized: GraphPad InStat 3 (2003, San Diego, USA – www.graphpad.com); Excel MS XP (2005 Microsoft).

RESULTS

The patients analyzed were 308 females and 120 males, who could be classified as three sub-groups: with non-stroke neurological manifestations with aPL (174, 40,7%), with non-stroke neurological manifestations without aPL (164, 38,3%), without non-stroke neurological manifestations but with aPL (30, 7%).

There have been analyzed in this study the syndromes that could be classified according to the International Headache Society (IHS).

There are two frequent types of headache in the studied groups: migraine and tension headache. Anyhow, there are a number of patients with „non-specific" headache and this may be due to an incomplete medical history. When it was possible, this type was considered tension headache. However, we identified patients with headache secondary to conditions like intracranial hypertension or cerebral vein thrombosis, which can be aPL-associated.

Prevalence of headache in the studied group

A number of 203 patients (60%) from those with neurological disorder complain at least once on the admission in the hospital of headache, at that moment of in the last 12 months (figure 1).

The highest prevalence of headache was noted among patients with systemic lupus erythematosus (SLE): 102 patients (61% from all SLE patients) had headache as complain at least one admission. This percentage is similar to those mentioned by other authors (4).

Main types of headache

Migraine was found in 39 cases (24,5% of all SLE patients, and 19,2 % of SLE with headache patients); common migraine was most often encountered, and only 11 patients from 39 had migraine with aura. For 29 (74,3%) of them there were proved associated cerebral or retinal vascular ischemic changes.

Tension headache was encountered in 53 patients (33% of all SLE patients, and 26% of SLE patients with headache). They had frequently depression (34 cases) or degenerative cervical spine involvement (46 patients). In more thant half of the cases,a reactive origin of the headache has been speculated. 6 patients have had in the medical history cerebral arterial occlusions.

Acute headache, without prodroma was found in 10 cases, and revealed severe damage of central nervous system: 4 patients had cerebral edema because of idiopathic intracranial hypertension (4%), 1 had cryptococcal meningitis (1%), and 5 had cerebral thrombophlebitis (5%).

Prevalence of aPL

SLE. Antiphospholipid antibodies had been detected in 22 of migraine patients (aCL in 11 patients, LA in 9 patients, and both antibodies in 2 patients), in 26 of the patients with tension headache (aCL in 21 patients, LA in 3 patients, both antibodies in 2 patients), and in 4 patients with cerebral thrombophlebitis (3 aCL and LA in constant positive titers at repeated assay). Despite the small number of patients, it is notable that 19 of 22 migraine patients with aPL had at least one ischemic event, cerebral or retinal, diagnosed clinical or by imagistic methods, and 8 of them had APS (6 with migraine and 2 with tension headache). 12 patients with tension headache and aPL had radiological ischemic cerebral lesions, with or without clinical history of ischemia, but in only 14 of 26 (53%) a CT cerebral scan was performed.

All of the 6 patients with *Horton arteritis* complain of headache, two temporal and the others diffuse. All of them underwent ischemic events, related to their underlain disorder. 4 of them had antiphospholipid antibodies detected. The pathogenic role of these antibodies regarding the neurological manifestations of Horton arteritis is controversial and has been discussed in the literature (5). 6 patients had retinal (3 cases) and cerebral (3 cases) infarctions, but only one of them had aCL in the serum at the second assay. In the other cases of positive antibody titers (3 with aCL antibodies, 1 with LA, 1 with both aCL and LA), the repeated

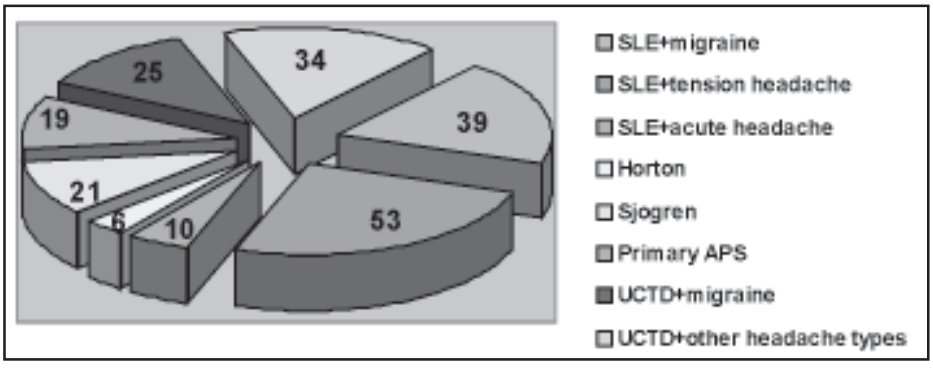

Figure 1
Headache and inflammatory connective tissue diseases in the study group

UCTD = Undifferentiated connective tissue disease

testing failed to demonstrate the constant presence of aPL in the patients blood, at least until they have been enrolled. In consequence, the pro-ischemic role of aPL in these patients is not clear. Their pathogenic role in these patients, who did not underwent an infectious disease potentially inductive for antiphospholipid antibodies in the 3 months preceding the diagnosis, is debatable, since they can be the result of lesions of the vascular endothelium.

In patients with *Sjogren syndrome* the headache occurred in 38% (8 from 21). In one patient the headache appeared after aseptic meningo-encephalitis. However, it is important to notice the high prevalence of aPL in these patients with sicca syndrome: 6 had aCL, 2 had LA and APS and ischemic cerebral lesions found by CT scan. Although the small size of the studied group diminishes the result signification, we can say that 75% of Sjogren patients with migraine have aPL in their serum and the high prevalence of migraine in these patients was observed by other studies (6).

One of the patients with *Wegener's granulomatosis* complained of headache secondary to sinusitis, but no aPL were found. Headache is the less severe of the neurological manifestations occurring in this disorder and is often secondary (7).

There were 59 (73,75%) from the group of patients with *undifferentiated connective tissue disease (UTCD)* complaining of headache: 25 with migraine, 3 secondary to sinusitis, 2 accompanying cerebral edema, 29 patients with non-specific, mainly tension headache. As the collagen-vascular disease is not classified, it is difficult to make considerations about the specific prevalence of headache, but 29 (49,1%) patients had aPL, of which 15 with migraine (24% of patients with this disease and headache) and 19 with tension headache (32,2%). In the group of 15 patients with migraine and aPL, 7 had cerebral ischemic lesions. Among the 10 patients without aPL, 4 had ischemic lesions. 11 patients with tension headache had ischemic lesions, but only 5 of them with aPL, with associated clinical event in 2 patients with ischemic stroke (one of which with APS).

In *primary antiphospholipid syndrome (PAPS),* headache occurred in 19 of 38 patients (60,5%): 7 with migraine (18,4%), 10 with tension headache (18,4%), 1 secondary to ischemic sylvian stroke and 1 with a high cervical spine discal protrusion. This prevalence of headache is similar to the data from other studies (8).

The association between aPL and headache

A number of 107 of 203 (52,7%) studied patients with autoimmune disorders had antiphospholipid antibodies with positive titers detected at least once. It is obvious that this must not be understood as a specific association, as long as pathogenic mechanisms producing headache are different in each of the studied diseases.

However, it's worthy to note that 50 of the 72 (69,4%) patients with migraine had aPL and 13 of them had APS. That means a higher prevalence of aPL in migrenous patients with collagen-vascular disease than in general population with migraine (9). This observation could be of some importance, suggesting that the finding of aPL in a patient with migraine suspected to bear a collagen-vascular disease can be an argument to sustain the existence of the immune disease. More studies are necessary in order to clarify the importance of the association as predictor of systemic disease.

There are no data in the studied group about the occurrence of ischemic stroke following „complicated migraine" or about the existence of focal deficits („aura without migraine"). Either their occurrence was not noticed or was lacking or, more probable, the patients were labeled as transient ischemic events or crisis. Therefore, considerations about the association between this manifestations and aPL cannot be made in the studied group.

DISCUSSION

1. State of knowledge

Migraine and SLE

The high incidence of headache, especially migraine, in SLE patients suggested its association with aPL. 52% of SLE patients have headache and 31% of them fulfill the criteria for migraine of International Headache Society (10). On the other side, there is a high prevalence of aPL in SLE patients, (40-50%), so the association aPL – migraine can be casual.

The pathogenesis of headache in the presence of aPL is unknown. Many possible mechanisms were incriminated. The interaction between aPL and phospholipidic endothelial membranes could induce the migraine crisis; aPL may induce a disregulation of the immune system and this can play a role in chronic headache; since platelets can produce algogenic substances, aPL can be a marker of platelet membrane lesions in some patients with migraine, while in „healthy" migrainous people aPL don't seem to interfere with the further evolution (11).

Migraine, aPL and SLE

Although recent data revealed that aPL prevalence is higher in SLE patients with migraine (all types)

than without migraine, studies failed in demonstrating a correlation aPL – migraine in SLE (12). Neither the frequency and severity of migraine, nor preceding aura significantly differ between aPL and non – aPL SLE sub-groups (10,13,14).

Migraine and aPL in non-SLE patients

This association has been studied either monitoring the neurological disorders in patients with aPL immunoreactivity, or searching the prevalence of aPL in populations with migraine (11). The largest case control study to date has failed to demonstrate an association of aCL immunoreactivity in patients less than 60 years of age with either migraine with aura, migraine without aura, or transient focal neurological events compared with controls. Even the results of the medical literature are contradictory, depending on the number of patients and the criteria used to define migraine, there are not any differences between positive and negative aPL sub-groups regarding clinical signs, frequency of migraine. aPL immunoreactivity doesn't seem to increase the short-time risk for stroke in migrainous people (14).

Transient focal deficits („aura without migraine") and aPL

Tietjen and colleagues, in 1993, demonstrated in their study that about 43% of the patients with transient focal deficits enrolled, with or without migraine, had aPL immunoreactivity, also having a poor family history of headache and a higher frequency of retinal or sensitive half-body transient deficits (15). Another study of his team in patients with transient focal neurological events, revealed an association of anticardiolipin antibodies (aCL) with negative family history for stroke and diabetes mellitus and briefer spells. Neuroimaging studies showed that permanent focal damage was more frequent in aCL immunoreactive patients despite the fact that neurological symptoms were transient. Interestingly, the short-term risk of stroke or other thromboembolic events in the presence of aCL was not similarly increased but this could be due to the the short follow-up period (14).

Migraine and antiphospholipid syndrome (APS)

In the past 20 years, there are data from numerous studies that suggest a high frequency of severe headache of migrainous type in primary and secondary APS, but statistics data didn't show any association between them. Clinical observation revealed improvement of headache by anticoagulants administered for other indication in APS, but also in non-APS patients (16). Neither the specificity of migraine for APS was clarified since it is very frequent in the general population. Although the association migraine – APS wasn't proved by large patient studies, it may be possible for a sub-population with features that need to be defined (2).

aPL and „ migrainous" ischemic stroke

Migraine-associated ischemic stroke is rare and is a certitude for some authors. The analysis of this association in which the stroke is a complication of the migraine, is not an aim of this presentation. Silvestrini and colleagues found aPL immunoreactivity in 6/16 patients with migrainous cerebral infarction (17). None of these patients had SLE, but all had other risk factors for stroke. These data highlight the importance of considering the presence of aPL in migrainous stroke.

2. Personal contribution

The increased prevalence of headache in SLE is controversial (9). Case-control studies did not demonstrate a higher incidence of headache (all types) in SLE comparing with general population (12).

However, there are some authors that suggest an association between headache and cerebral ischemia in SLE greater than the degree of association between SLE and headache in patients without ischemia, and on the other side a higher prevalence of antiphospholipid antibodies in SLE patients with headache (all types) than in those without headache. This considerations need to be clarified in the future (12, 18).

In our study, 74,36% of the SLE patients with headache had associated cerebral ischemia and more than half of them had aPL. Two possibilities can be raised: either the association between aPL, headache, ischemia and SLE does not exist, and the results of our study are incidental, or it exist for a sub-group of patients, for instance those with lupic vasculopathy or arterial occlusion determined by other causes. Even in the last sub-group (patients with SLE, cerebral ischemia and aPL), it might exist different sub-types of patients more or less at risk to develop migraine. Thus, it is recommended to search for aPL in headache (especially migraine) patients with SLE. It is mandatory to do the assay in SLE with ischemia, with or without migraine.

The association aPL – cerebral thrombophlebitis was expected and is more clear in the study group. In this case, headache is secondary. aPL should be searched in patients with cerebral thrombophlebitis, since this event can reveal APS. It is worthy to note that headache was the only complaint that revealed the venous thrombosis in two patients, papillary edema was present only in one patient (25%!), and in a patient with superior longitudinal sagital sinus thrombosis it was accompanied only by encephalopathy, without other signs of localization. This

invites to consider acute headache in SLE as a sign for the appearance of a new neurological event (19).

Statistical analysis

We analyzed the associations between aPL and headache, migraine, as the presence of ischemic brain lesions in aPL patients with headache.

In the studied population, headache (all types) is not significantly associated with aPL: P = 1.0000, Odds ratio= 1.008, 95% Confidence Interval: 0.6876-1.479 (figura 2a).

On the other hand, the association between migraine and aPL is statistically significant: P = 0.0186, Odds ratio = 1.941, 95% Confidence Interval: 1.128-3.342 (figura 2b).

If we analyze the association between headache and cerebral ischemia in patients with headache, we don't find a significant association: P = 0.5512, Odds ratio= 1.205, 95% Confidence Interval: 0.6654-2.182 (headache all types) (figure 3a).

In migraine patients, clinical or radiological cerebral ischemic lesions had been identified in 38 (76%) of patients with migraine. These important figures do not have statistical power: P = 0.2083, Odds ratio = 1.995, 95% Confidence Interval: 0.7200-5.526. However, the trend of the confidence interval show a potential risk role of the association, masked by the lack of statistical power due to the little number of patients studied (figure 3b).

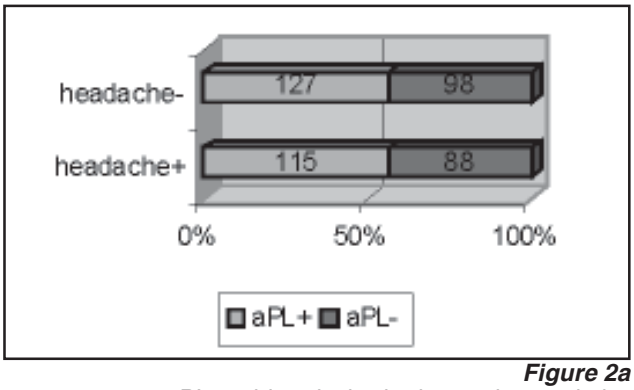

Figure 2a
aPL and headache in the study population

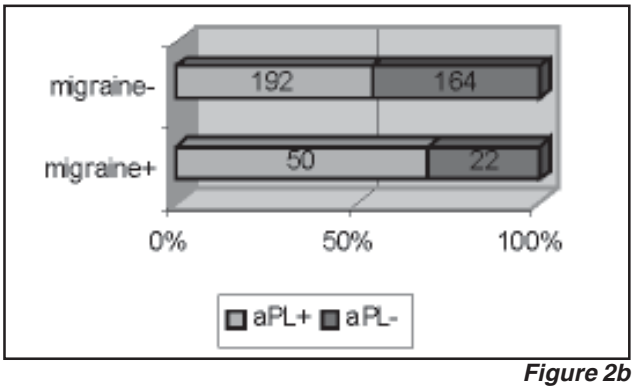

Figure 2b
aPL and migraine in the study population

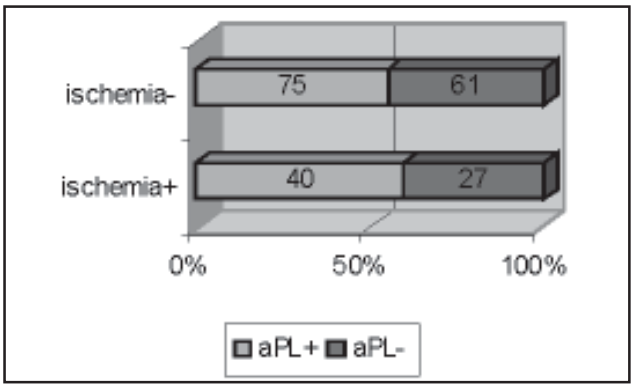

Figure 3a
The association aPL-cerebral ischemia in headache patients

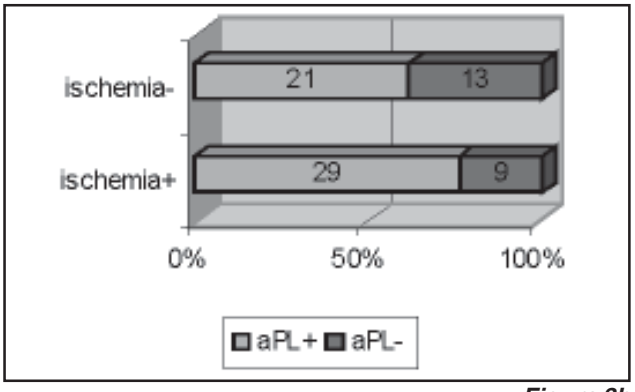

Figure 3b
The association aPL-cerebral ischemia in migrenous patients

We looked for the association aPL-brain ischemia in patients with headache for the main immune mediated diseases. This kind of approach was not possible for all collagen immune diseases, due to little number of patients or lack of brain radiological exams.

In SLE patients, the association aPL-brain ischemia can not have a correct evaluation, since 39 patients with tension headache had not brain CT scans. However, even we consider these patients without any cerebral ischemic lesion, we obtain a strong association between aPL presence and cerebral ischemia in headache patients (all types): P < 0.0001, Odds ratio = 5.860, 95% Confidence Interval: 2.486-13.814.

If we substract the patients without CT scan, we obtain a significant association: P = 0.0043, Odds ratio= 8.364, Confidence Interval 95%: 1.951- 35.845 (SLE patients with headache, all types) (figure 4a).

For the SLE patients with migraine, there is a significant association between aPL and cerebral ischemia: P = 0.0055, Odds ratio= 9.048, 95% Confidence Interval: 1.912-42.824. The trend of the Confidence Interval suggests that the association power will increase for a larger studied group (figure 4b).

In patients with UTCD, a systematic error factor represented by the lack of cerebral radiological exams makes impossible a correct approach of the associations studied.

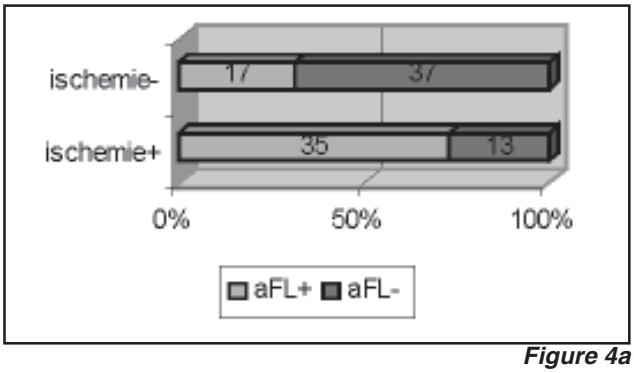

Figure 4a
The association aPL-brain ischemia in headache patients with SLE

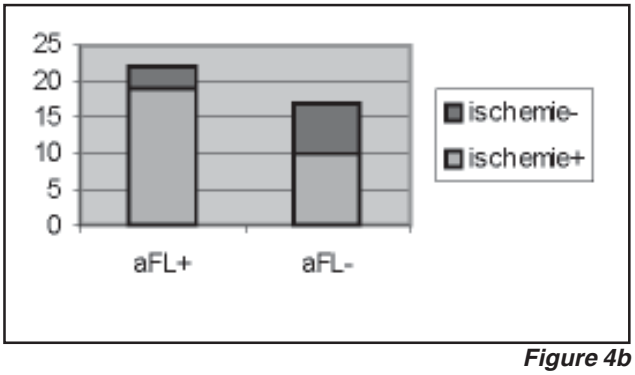

Figure 4b
The association aPL-brain ischemia in migraine patients with SLE

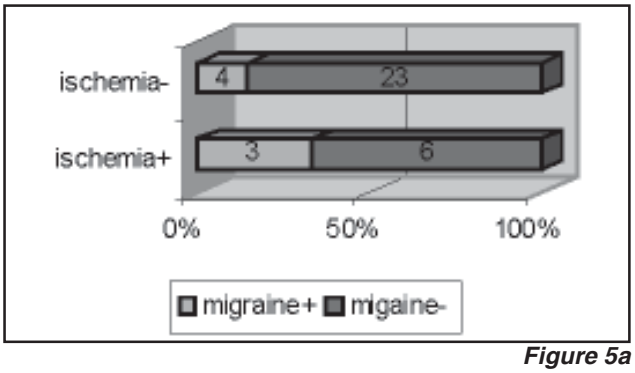

Figure 5a
The association migraine-cerebral ischemia in PAPS patients

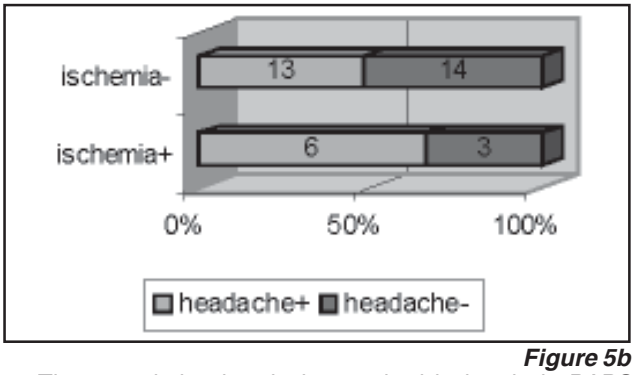

Figure 5b
The association headache-cerebral ischemia in PAPS patients

In patients with Sjogren syndrome and headache, there is no significant association between aPL and ischemic brain lesions, even thou this seem to be related to the small studied group (Odds ratio = 2.778, 95% Confidence Interval: 0.09195-83.915).

In patients with PAPS, headache can be found in more than half of them (55%). Migraine is present in 32%. Ischemic lesion can be found in 47,37% of all patients with PAPS and 15,8% of patients with headache.

Headache (all types) and migraine are not significantly associated with cerebral ischemia in patients with PAPS: P = 0.4513, Odds ratio = 2.154, 95% Confidence Interval: 0.4443-10.442, respectively P = 0.3327, Odds ratio = 2.875, 95% Confidence Interval: 0.5014-16.484 (figure 5a,b).

However, the limits of Confidence Interval suggest that the power of the association is limited by the little dimensions of the study group. Overall, there is no significant difference between SAPS and PAPS in what concerns the prevalence of headache.

We can conclude that migraine alone, not headache all types, is significantly associated with aPL in patients with systemic immune disease. In SLE patients, headache (all types) is significantly associated with positive titers of aPL, and cerebral ischemic lesions are significantly encountered. However, the power of the association aPL – ischemia – migraine can be masked by the small size of the sample studied.

The heterogeneity of headache distribution and the variety of studies results can be explained by the different and various mechanisms producing headache. In SLE patients, both aPL and headache are frequent, so their association can be unrelated to a pathogenic role of aPL in producing headache. On the other hand, there may be a group of patients in which the association aPL-headache, especially migraine, can be relevant.

The triple association aPL positive titers – migraine – ischemia rises the question of the underlain mechanisms. The scenario can be one of the following situations:

- the disease produces aPL and migraine, one of them or the disease produce cerebral ischemia;
- aPL induce migraine and the latter one is associated, by an aPL-independent mechanism, with ischemic lesions;
- aPL are involved in the occurrence of ischemia and migraine;
- aPL produce ischemia, which can produce, within an unknown mechanism, migraine.

In the latter two situations anticoagulants are the option with no doubt, as aPL act in their thrombophilic manner. In the first two, the attitude is considering the mechanism of ischemic lesions. In the first case, if aPL determine cerebral ischemia, anticoagulant is a logical choice, but the mechanism is sometimes difficult to prove. In the second case, if aPL are the

cause of migraine, in an ischemic fashion, anticoagulant is also the option. In this case, studies have to be made, to search if ischemic lesions are more frequent in the presence of aPL in patients with migraine without stroke but with systemic autoimmune disease.

The association migraine-stroke has been shown by many studies that analyzed the predictive role of sex, family history of migraine, oral contraceptives, vascular risk factors (20, 21, 22, 23, 24).

aPL are risk factor for ischemic stroke and, consequently, aPL and migraine together in the same patient have a certain risk for cerebral ischemic lesions.

There are studies that suggest a greater risk to develop ischemic stroke for women with migraine, and this seem related to APS. Surprisingly, headache disappears when they are treated with anticoagulants for the thrombotic events generated by the APS (25).

More controversial is the situation of patients with migraine without demonstrable thrombotic events. In these, anticoagulant therapy is debatable, considering the hemorrhagic risk. Some suggested the use of low molecule weight heparin, but a double blind trial failed in demonstrating any effect in treating patients with chronic headache and aPL (16), maybe because they included patients with chronic headache (all types), not only migraine (26). Despite the lack of support offered by an evidence-medicine approach, there is still a trend to treat migraine patients with aPL with anticoagulants, but is not clear whether there is a subgroup of potential responsive patients (27).

According to all of this data, we suggest that the search for aPL in patients with migraine can be useful. aPL is an accepted vascular risk factor, and consequently cerebral ischemia have to be searched.

It is maybe worthy to look for cerebral ischemia in patients with chronic migraine and aPL. Even we don't advocate the use of anticoagulants in any patient with migraine, in patients with chronic migraine and constant aPL positive titers, changes in headache characteristics, the appearance of new MRI small cerebral ischemic lesions, the constant presence of aPL can be discussed as arguments in favor of anticoagulant therapy. Further studies are necessary to identify a risk population for ischemic stroke among patients with migraine and aPL, but also to identify a subgroup of anticoagulant – responsive migrainous patients with positive titers of aPL. Finally, we have to emphasize the possible influence of a specific subtype of aPL on the results. Studies have to precise the place of aPL subtypes in association with headache, especially migraine.

From the practical point of view, one can ask if it is beneficial to look for aPL in patients with migraine and autoimmune disease, or in patients with migraine without underlying disease?

The answer to the first question is yes: as soon as we are in front of a systemic autoimmune disease with neurological manifestations, all mechanisms that can explain systemic involvement, including APS, have to be taken into account. The serologic assay must be accompanied by correct radiological investigations (MRI). Others cause to explain headache and the presence of aPL (drugs, infections) have to be ruled out.

Non-ischemic neurological syndromes occurring in young patients are a signal for possible underlying disease. It is thus mandatory to look for the presence of aPL not only to explain the neurological complaints, but to evaluate the risk of ischemic events or developing a systemic disease. On the other hand, the occurrence of a non-stroke syndrome in the presence of aPL urges to look for a silent ischemic cause for the event and for the features of a systemic disease that can explain the both the clinical and biological disturbances.

This double-signal character of the association aPL-migraine emerges from this study. The statistically significant presence of ischemic lesions in SLE patients with migraine and aPL positive titers, suggest that this must not be considered firmly non-ischemic and antithrombotic therapy to be a valid option. Further studies are needed to clarify this issue.

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