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ORIGINAL ARTICLE

Antiphospholipid antibodies in HIV-positive patients

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Abstract Antiphospholipid (aPL) antibodies classically have been associated with thrombotic phenomena and abortion in patients with autoimmune diseases. The objective of the present work was to evaluate the frequency of such antibodies in patients infected with HIV and study its association with the presence of clinical manifestations of antiphospholipid syndrome (APS). Using a transversal study, a population of patients diagnosed with HIV, identified through an enzyme-linked immunosorbent assay (ELISA) test and confirmed by Western blotting, aged above 17 years old, was investigated. Through a standard questionnaire, the presence of APS manifestations was investigated, as well as the frequency of rheumatic manifestations. Antibodies against β2 glycoprotein I (anti-β2 GPI) and anticardiolipin (aCL) IgA, IgG, and IgM were investigated by the ELISA method using commercial kits (QUANTA Lite, INOVA Diagnostics). Ninety patients were studied, 47 (52.2%) male and 43 (47.8%) female. Clinical manifestations of APS were detected in 12 patients (13.3%) of the studied population, whereas arthralgia was the most common rheumatic manifestation (38.9%). Of the 90 patients, 40 (44.4%) were reactive for at least one type of aPL antibody (aCL and/or anti-β2 GPI). The frequency of aCL was 17.8%, from which 15 (16.7%) had aCL IgG, 3 (3.3%) IgM, and 1 (1.1%) IgA. The frequency of the anti-β2 GPI antibody was 33.3%, from which 29 (32.2%) were positive for isotype IgA, 4 (4.4%) isotype IgM, and 1 (1.1%) isotype IgG. No association was observed between immunoreactivity for aPL antibodies in general or each isotype in particular and the presence of APS manifestation. In the present study, it was possible to observe a relatively high frequency of aPL antibodies, particularly for isotype IgA anti-β2 GPI in HIV. However, there was no association to APS manifestations, suggesting that such antibodies had

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no etiopathogenic role in these complications in patients with such retroviral infection.

Keywords Antiphospholipid antibodies · Antiphospholipid syndrome · HIV · IgA

Introduction

Antiphospholipid (aPL) antibodies are frequently associated with thrombotic phenomena and repeat abortions in patients with autoimmune diseases (AID). This is particularly prevalent in patients with systemic lupus erythematous (SLE), characterizing a condition referred to as antiphospholipid syndrome (APS) [1]. These antibodies have also been described in various bacterial infections such as syphilis, tuberculosis, endocarditis, and others [2, 3], as well as in viral infections such as parvovirosis [4, 5], hepatitis [6–9], and retrovirosis [10–18]. In contrast to what occurs in autoimmune conditions, the presence of these antibodies during infections is usually not associated with clinical complications of APS, although isolated reports of thrombotic associations in some patients with HIV have been published previously [19–22]. The reasons for why the presence of aPL antibodies in infectious diseases is not commonly associated to thrombosis are not totally known. A series of studies suggests that, in infectious diseases, the aPL antibodies are specific for isolated phospholipids, whereas in AID, its specificity is for phospholipid and at least one plasmatic protein with anti-coagulant activity (β2 glycoprotein I—β2 GPI). The inhibition of such a protein could predispose to thrombophilia [23]. The objective of the present work was to evaluate the frequency of anticardiolipin (aCL) antibodies and anti-β2 GPI in patients infected with HIV as well as to study its association with the presence of clinical manifestations of APS.

Materials and methods

Study design A transversal study was used to investigate a population of patients diagnosed with HIV.

Study population The study population was composed of studied patients diagnosed with HIV, as identified by enzyme-linked immunosorbent assay (ELISA) test and confirmed by Western blotting. They were all aged above 17 years old and identified during the period from August to December 2005, derived from various services, public or private, and sent by their physicians to the Retrovirus Laboratory of the Infectology Service–University Hospital Prof. Edgard Santos (HUPES). The project was approved by the Ethics in Research Committee of the HUPES.

Data obtainment strategy Patients were selected when they sought the Retrovirus Laboratory to perform tests for viral charge and CD4/CD8 cell counts. After agreeing to participate in the research and signing the Free and Informed Consent form, an interview was administered by using a questionnaire related to rheumatologic symptoms and the presence of thrombotic and/or obstetric complications. For those with a positive history of thrombotic and/or obstetric complications, the patient's record was reviewed to complement the information.

Laboratory tests The blood samples were collected in a tube with ethylenediaminetetracetic acid, and aliquots of 1-ml plasma for each patient were frozen at −20°C until the tests took place for aPL antibodies. Such search was performed by ELISA method for aCL antibodies (IgA, IgG, and IgM) and anti-β2 glycoprotein I (IgA, IgG, and IgM) using commercial kits (QUANTA Lite, INOVA Diagnostics), and expressed in units, according to the manufacturer's instructions. For aCL, the results are presented semi-quantitatively in APL, GPL, and MPL units for IgA, IgG, and IgM, respectively, from a standard curve of 5 points. Values below 20 U are negative, between 20 and 80 U are weak positive to moderate, and above 80 U, strongly positive. For anti-β2 GPI, the results are presented semi-quantitatively in units SAU, SGU, and SMU for IgA, IgG, and IgM, respectively, from standard curve of 5 points. Values below 20 U are negative and above 20 U positive. At the same time, tests for hepatitis B surface antigen (AgHbs), anti hepatitis C virus (HCV), anti human T-cell leukemia virus type I (HTLV-I) were performed to evaluate the presence of co-infections. All these tests were performed at the Immunology Laboratory of the Faculty of Pharmacy at the Federal University of Bahia.

Statistical analysis The SPSS 9.0 package was used for statistical analysis. Values were expressed as means plus standard deviation or median. For analysis of the association between qualitative variables, the chi-square or the Fisher exact test was used. The results were considered statistically significant when $p<0.05$.

Results

One hundred and twenty patients infected with HIV were invited to participate in the study. However, only 90 accepted to participate by signing the Free and Informed Consent form.

Of the 90 patients, 47 (52.2%) were male and 43 (47.8%) female; 25 (27.8%) were white and 65 (72.2%) non-white, and the mean age was 38.03±9.67 years

Table 1 Demographic data of the 90 patients with HIV

Characteristics	*n* (%)
Sex	
Male	47 (52.2)
Female	43 (47.8)
Race	
Whites	25 (27.8)
Non-whites	65 (72.2)
Mean age (years)	38.03±9.6

(Table 1). Among the 30 patients who did not consent to participate in the study, 19 (63.3%) were male and 11 (36.7%) female; 20 (66.7%) were non-white and 10 (33.3%) white, and the mean age was 39.2±10 years. There wasn't any significant difference in the major demographic variables between the patients who participated and those who did not consent to participate in the study.

Table 2 shows the characteristics related to infection by HIV of the 90 patients.

Fifty-one patients (56.7%) presented at some point in their disease clinical manifestations of acquired immunodeficiency syndrome (AIDS), characterized by gastrointestinal, respiratory, and neurological symptoms, Kaposi sarcoma, or opportunistic infections.

Table 3 shows some of the clinical manifestations related to the rheumatologic syndromes commonly described in the context of HIV infections. No patient presented an arthritic condition in their history or as evidenced by physical examination.

Clinical manifestations of APS were detected in 12 patients (13.3%) of the studied population, 7 patients (7.7%) had at least one thrombotic complication, and 7 patients (7.7%) had at least one obstetric complication (Table 4).

Table 2 Characteristics related to infection by HIV in the 90 patients studied

Characteristic	*n* (%)
AIDS	51 (56.7)
Time of diagnosis in months (md)[a]	48 (24–84)
Viral load[b]	
≥1,000	75 (83.3)
<1,000	15 (16.7)
CD4 counting[c]	
<200	12 (13.3)
200–499	36 (40.0)
≥500	42 (46.7)
Anti-retroviral treatment (HAART)	68 (75.6)
Co-infection	
HTLV-I	6 (6.7)
Hepatitis B	4 (4.4)
Hepatitis C	7 (7.8)

[a] Median plus quartile values 25 and 75
[b] Copies of RNA/ml
[c] Cells/mm^3

Table 3 Frequency manifestations related to rheumatologic syndromes in the 90 HIV patients

Manifestation	*n* (%)
Arthralgia	35 (38.9)
Xerostomia	29 (32.2)
Xeroftalmia	28 (31.1)
Myalgia	16 (17.8)

Frequency of aCL antibodies and anti-β2 GPI

Of the 90 patients infected with HIV, 40 (44.4%) had at least one type of aPL antibody (aCL and/or anti-β2 GPI). The frequency of aCL was 17.8% with 15 (16.7%) positive for aCL IgG, 3 (3.3%) for the isotype IgM, and 1 (1.1%) for aCL IgA. Weak-to-moderate titers were observed in 14 patients (15.6%) with isotype IgG and in 3 patients (3.3%) with isotype IgM and a strong titer in 1 patient (1.1%) with isotype IgA and 1 (1.1%) with isotype IgG (Fig. 1).

The frequency of anti-β2 GPI antibodies was 33.3%, with 29 (32.2%) positive for isotype IgA, 4 (4.4%) isotype IgM, and 1 (1.1%) isotype IgG (Fig. 2).

Antiphospholipid antibodies and clinical manifestations of APS

As described above, only 12 (13.3%) patients had at least one manifestation of APS at some point during their disease. However, there was no statistically significant association between the presence of such manifestations and the presence of at least one of the aPL antibodies tested

Table 4 Frequency of HIV patients with at least one clinical manifestation of APS

Clinical manifestation[a]	No. of patients (%)
Thrombotic events	7 (7.7)
Venous thrombosis	2 (2.2)
AMI	2 (2.2)
Stroke	2 (2.2)
Superficial phlebitis	2 (2.2)
Arterial thrombosis	1 (1.1)
Obstetric events	7 (7.7)
Fetal loss[b]	5 (5.6)
Premature birth[c]	3 (3.3)

AMI Acute myocardic infarction
[a] Four patients had more than one thrombotic and/or obstetric event
[b] Fetal loss more than 10 weeks
[c] Premature birth less than 34 weeks

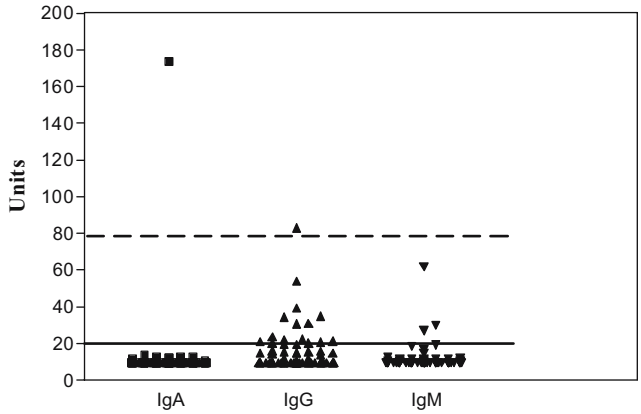

Fig. 1 aCL antibodies in 90 HIV patients

in the population studied nor with the presence of a particular aPL isotype.

Similarly, when the presence of thrombotic or obstetric complications was analyzed separately, no association was identified with the presence of aPL antibodies, together or isolated.

Symptoms of APS and the use of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs)

As we did not observe an association between the presence of thrombotic complications and aPL antibodies, an analysis was made to evaluate the association of these complications with the use of antiretroviral therapies. It was noted that the presence of such complications was not associated with the use of each antiretroviral drug in particular. Also, when the association between thrombotic phenomena and the use of any antiretroviral therapy in general was evaluated, no statistical significance was found (p=0.280).

Co-infections and the presence of aPL antibodies

The study of aPL antibodies in co-infected patients demonstrated the presence of aCL in two cases (33.3%) with HTLV-I, two (28.6%) with HCV, and one (25%) with hepatitis B and anti-β2 GPI in two cases (50%) with hepatitis B, two (28.6%) with HCV, and one (16.7%) with HTLV-I, whereas the presence of clinical manifestations of APS was detected in one patient (16.7%) with HTLV-I and one patient (14.3%) with anti-HCV. There was no statistically significant association between the presence of aPL antibodies or manifestations of APS and the existence of co-infections (p=0.184 and p=1,000, respectively).

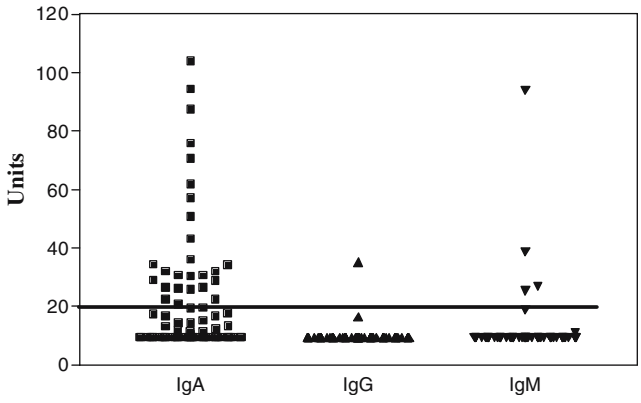

Fig. 2 Anti-β2 GPI antibodies in 90 HIV patients

AIDS vs the presence of aPL antibodies and APS

There was no association between AIDS and aCL or anti-β2 GPI antibodies (p=0.591), regardless of the isotype IgA, IgG, and IgM (p=0.430 and p=0.178, p=0.492 and p=0.563, p=0.604 and p=0.415, respectively). However, an association between symptomatic patients for AIDS and those symptomatic for APS was revealed (p=0.045).

Viral load, CD4 lymphocytes counting vs the presence of aPL antibodies and manifestations of APS

There was an association between charge viral load ≥1,000 and aPL total (p<0.001), anti-β2 GPI in general (p=0.005), and anti-β2 GPI IgA (p=0.002).

There was no association between CD4 count <200 or ≥500 and aPL antibodies in general (p=0.677 and p=0.119, respectively), aCL antibodies alone (p=0.130 and p=0.055, respectively) neither anti-β2 GPI (p=0.511 and p=0.654, respectively).

Also, there was no association between viral load or CD4 count and manifestations of APS.

Discussion

Historically, aPL antibody was linked to infection with the development of Wassermann's reaction for syphilis more than a century ago. Thereafter, it was observed that patients with AID could have false-positive reaction for syphilis and that such patients would have a higher incidence of thrombotic phenomena and/or repeated abortions. Other historical landmarks in this area were the description of a lupus anticoagulant (LA), the development of a radioimmunoassay test for the detection of aCL antibody, and the finding of the existence of a co-factor (β2 GPI) necessary for linking these antibodies to their antigen [23]. More recently, criteria were established for the classification of an APS [1].

The detection of antibodies directly against co-factor β2 GPI has also been considered as a marker for APS, suggesting a higher specificity than aCL antibodies. Such findings motivated its addition to the recently published APS criteria [24]. On the other hand, work done in our

service in collaboration with the group of the Morehouse School of Medicine, Atlanta could not confirm the specificity of anti-β2 GPI antibodies [2].

Although various studies have confirmed the association of aPL antibodies with thrombotic/obstetric phenomena in AID, particularly in SLE, there have been publications showing its presence in infectious diseases, but generally not associated to the presence of the above complications. As early as 1989, Taillan et al. [25] described the presence of LA in about half the patients infected with HIV. Afterwards, various other studies, including some derived from our service, showed the presence of such antibodies in infectious diseases [26–30].

Recently, there have been studies published in the literature suggesting the participation of aPL antibodies in the development of thrombotic complications in HIV patients [31–33], which motivated the initiation of this study. In this work, a prevalence of clinical manifestations of APS at 13.3% was observed, as well as a prevalence of aPL antibodies of 44.4%, of which 17.8% was aCL and 33.3% anti-β2 GPI antibodies. However, the presence of aPL antibodies was not associated to clinical manifestations of APS.

This figure slightly differs from those obtained by Palomo et al. [17], who found a frequency of 12.7% aCL and 6.3% anti-β2 GPI in a population of 63 patients infected with HIV in Chile, and from the study conducted by Loizou et al. [34], where a prevalence of 7% was found for aCL and 6% for anti-β2 GPI in a population of 100 black patients from South Africa. Such differences can be attributed to methodological reasons or to differences in genetic backgrounds of the populations studied. In the work performed by Palomo et al. [17], which had a similar design to ours, the presence of aPL antibodies in patients with HIV was also not associated to clinical manifestations of APS.

Because no association between the presence of thrombotic phenomena with aPL antibodies was observed, the possibility of such complications being associated to the use of antiretroviral therapy was considered, particularly PIs [35]. However, the analysis did not show any association with the use of such drugs. These data suggest that other thrombogenic factors, such as deficiency of protein C and S of the coagulation or the increase in platelet activation, not investigated in the present study, could have participation in the appearance of thrombotic manifestations in patients with HIV.

As previously described, aPL antibodies have been reported in other infectious diseases generally not associated to the presence of APS complications. However, there are reports of thrombotic complications in viral infections such as HIV and hepatitis C, virtually attributed to the presence of these antibodies [36]. The analysis of patients with co-infections (HTLV-I, hepatitis B, and C) revealed that there was no association with the presence of aPL antibodies or APS manifestations.

A secondary objective of our study was to evaluate, in a population of patients with HIV, the frequency of manifestations related to rheumatologic diseases such as Reiter syndrome [37], psoriatic arthritis [38], and Sjögren syndrome [39]. To this aim, we used a standard questionnaire with questions such as the presence of xerostomia, xeroftalmia, myalgia, arthralgia, and arthritis, besides the physical exam, in cases of positive responses. A high frequency of arthralgia was found (39.8%); however, no patient revealed the presence of arthritis or other manifestations that would characterize the clinical conditions described above. The frequency of arthralgia in patients infected with HIV has varied from 13 to 65% [40, 41] and could be attributed to the viral infection itself or to the medication used for its treatment.

A very curious finding of the present study was the higher frequency of anti-β2 GPI of IgA class (32.2%) antibodies. The role of the isotype IgA anti-β2 GPI in HIV infections is intriguing, as in another recently published study, this was the only isotype identified in patients with HIV [34]. Additionally, in a study regarding the presence of aCL antibodies in patients with the retrovirus HTLV-I, IgA aCL was the immunoglobulin most frequently identified [42].

Our observation that patients with viral load higher than 1,000 expressed a higher frequency of aPL antibodies. Such findings have not been previously published, and we hypothesized that it could represent a direct or indirect participation of such antibodies in virus clearance. Of note, we did not find any association between the presence of aPL antibodies and higher or lower CD4 counting. It might represent the inclusion of patients in different stages of the disease.

In conclusion, this is the first study that investigates the presence of aPL antibodies in patients with HIV in Brazil, and from this, it was possible to observe a relatively high frequency of such antibodies, particularly of isotype IgA anti-β2 GPI, without an association with APS manifestations. It suggests that, in HIV patients, such antibodies do not have an etiopathogenic role in these complications.

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