Original Article

Antiphospholipid Syndrome, Review of 24 Iraqi patients

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Summary:

Background: *Antiphospholipid syndrome (APS) is a disorder in which vascular thrombosis and / or recurrent pregnancy losses occur in a patient who has laboratory evidence of antibodies against phospholipids or phospholipids binding protein cofactor. Usually the patient presents at an age between 35-45 years, with equal male to female ratio. Mostly they present with thrombosis or pregnancy complication. A quarter of the patients have thrombocytopenia and about one fifth have hemolytic anemia. The diagnosis rests on the criteria set as the Revised classification criteria for the Antiphospholipid syndrome*

Patients and Methods; *During the period from 1st Jan. 2002 until the 1st Jan. 2006,24 patients who met the criteria of APS (according to Revised classification criteria for the Antiphospholipid syndrome) were included in the study.*

The diagnosis of deep venous thrombosis (DVT) was done by using Doppler study of the selected organ, while brain CT and magnetic resonance imaging were used to diagnose cerebrovascular thromboses.Serological evidence of APA were either an abnormal KCT and KCT index and/or a positive aCL antibody test on 2 occasions.

Results : *Three quarter of our patients were females, more than half of them aged 21-30 years ,54.16% of our patients presented with thrombosis the commonest site of which was DVT of lower extremities. Abortion alone was the presenting problem in two patients and two patients presented with thrombosis following abortion Another two patients presented with bleeding problems. Gathering the history; follow up abortion occurred in ten of the thirteen premenapausal married ladies, of whom five had more than three abortions.\Laboratory evaluation revealed anemia in 8 patients (33.33%) and thrombocytopenia in 5 patients (20.8%).The KCT and KCT index were suggestive of APS in 14 of the 23 patients tested (60.86%)and the aCL was positive in 15 of the 19 tested patients (78.94 %).*

Conclusion, *We think that our study, although small, highlights some of the clinical and laboratory findings of this syndrome in Iraqi patients, larger studies are needed for better evaluation..*

Key Words: *Antiphospholipid syndrome (APL), anticardiolipin antibodies(aCL).*

Introduction:

Antiphospholipid (APS) syndrome is a disorder in which vascular thrombosis or a recurrent pregnancy loss occurs in a patient who has laboratory evidence for antibodies against phospholipids or phospholipids binding protein cofactor(APA) (1).

In a large series of medical patients, 7% were APA positive and 2% fulfilled the criteria of APS (2). Among patients with SLE the prevalence of APA is much higher ranging from 12-30% for aCL antibodies, and 15-34% for LA(1,3).

The disorder is generally considered to fall in the category of autoimmune diseases (1). Patients generally present with thrombotic manifestations or pregnancy losses or complications The usual age of patients at the time of presentation with thrombosis is 35-45 years (1).Arterial and Venous Thromboembolic Disease affects up to 70% of patients in some series (4,5).Other manifestations include Thrombocytopenia , neurological syndromes, cardiovascular disorders,pulmonary disorders and others (6,7,8).

Approximately 15% of patients with recurrent pregnancy losses have APS (4,7,9) and in Iraqi women APA were detected in 34.5% of ladies with recurrent midtrimester abortion (4).

Catastrophic APS is defined by the clinical involvement of at least three different organ systems over a period of days or weeks, with histopathological evidence of multiple occlusions of large or small vessels (7).

Treatment decisions fall into prevention of further thrombosis of large vessels, and management of pregnancy in association with APA (2).

Long term treatment with oral anticoagulants is advised because of the high rate of recurrence even if the venous or arterial occlusion occurred before many years. The management of patients with APA and previous thrombosis remains contentious. Observational studies suggest that these patients should remain on indefinite oral anticoagulation maintaining an INR of 3-4.The management of recurrent fetal loss is based on the use of anticoagulation with heparin in combination with low dose aspirin (2,4).

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Patients and Methods:

Twenty four patients were recruited from hematology unit Baghdad teaching hospital for the period from the 1st of January 2002 to the 1st of January 2006. They were eligible if they had an objectively confirmed arterial or venous thrombosis and or recurrent pregnancy loss plus a positive test for APA on two occasions at least 12 weeks apart. All patients had detailed history and detailed physical examination including neurological examination. Investigation included CBC, ESR, PT, PTT, KCT and KCT index, ELISA test for aCL antibodies, ANA, urinalysis, liver function test and renal function test. Doppler study of the venous system of the lower limbs and portal venous circulation were done when venous thrombosis was suspected, and CT& or MR1 of the brain were done for patients with CNS manifestations.

The diagnosis of APS followed The *Revised classification criteria for the Antiphospholipid syndrome* shown below:

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met (7):

Clinical criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions or (ii) recognized features of placental insufficiency, or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Homeostasis (Scientific Subcommittee on LAs/phospholipids). 2.Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high liter (i.e. > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. 3. Anti-*B*2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in liter > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized EL 1 SA, according to recommended procedures.

Patients were treated with heparin and warfarin for definite thrombotic episodes, aspirin was used during pregnancy and for patients not responding to warfarin alone,while prednisolone,cyclophosphamide and azathioprine were used for patients with associated vasculitis and those with recurrent thromboses not responding to adequate anticoagulation as outlined in results.

Results:

Figures 1&2 show the main demographic features of our patients, 18 were females (75 %), 6 were males (25%) . More than half of study patients were in the third decade of their lives (58, 33%). Thirteen (54.16%) of our patients presented with thrombosis, another two (8.3%) presented with thrombosis following abortion. Two patient presented with abortion Two patients (8.3%) presented with bleeding tendency Another two patients had anemia at presentation. (Table 1) Thrombotic episodes occurred in 20 patients. The commonest site of thrombosis (shown in table 2) at presentation and during follow-up was the lower extremities ;occurring in 15 patients (62.5%).Seven of those 15 patients (46.66%) had more than two attacks of DVT. The next most common site of thrombosis was the portal venous system occurring in two patients (8.3%). The most common site of arterial thrombosis was the CNS. Table 3 showed that three patients (12.5%) had bleeding episodes, two were cutaneous and one was CNS bleeding (none was on anticoagulant or antiplatelets drugs before bleeding).

Abortion occurred in ten of the thirteen married premenapausal ladies (76.9%).Five of those ten ladies (50%) had more than three abortions. A total of 37 abortions occurred in those 10 ladies, 21(56.7%) in the fetal period, the other 16 (43.3%) abortions were in the prefetal period (Table 4). Laboratory evaluation shown on table 5 showed that 8 patients (33.3%) had anemia (i.e.; Hb less than 100G/L) Thrombocytopenia (i.e.; platelet count less than 100 $x10^9$/L) occurred in five patients (20.8%). Leucopenia occurred in three patients (12.5%) Erythrocyte sedimentation rate was more than 30 mm/hour in eleven patients (45.83%). PT was more than 13 seconds in seven patients (29.16%) and the PTT was more than 40 seconds in thirteen patients(54.16%).

The KCT and KCT index were abnormal in 14 of the 23 tested patients (60.86%) and the aCL antibody was positive in 15 of the 19tested patients (78.94%).The ANA was positive in nine patients

(37.5%).Urinalysis showed active sediment in four patients (16.66%).

Our treatment strategy was to control and prevent further thrombosis in a patient with history of thrombosis and to try to prevent fetal loss in a pregnant lady Treatment used was anticoagulation (heparin followed by warfarin) which we used for 14 patients (58,33%), we used high intensity anticoagulation(i.e. INR of 3-4) Aspirin was used for 16 patient (66.66%) not responding to warfarin alone and in pregnant ladies with history of thrombosis or fetal loss. Control of disease activity using prednisolone was used for 14 patients (58.33%) with recurrent thrombotic episodes inspite of anticoagulation and those with evidence of vasculitis starting with doses of 1 mg/kg body weight until response and then tapering to the smallest dose that is required to suppress disease activity.Additional immunosuppressant (cyclophosphamide or azathioprine) was used in six patients (25%) for uncontrolled disease activity by prednisolone and anticoagulants (Shown in table 6).

The majority of our patients are alive (23 patients; 95.8%) after a mean follow up of 39 months and we lost only one patient who died very early after diagnosis because of portal vein thrombosis and liver failure.

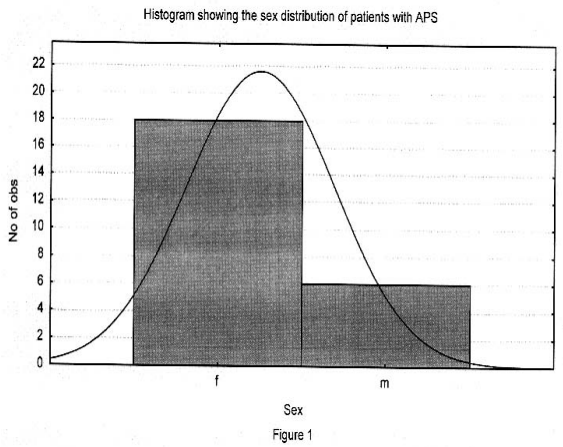

Figure 1

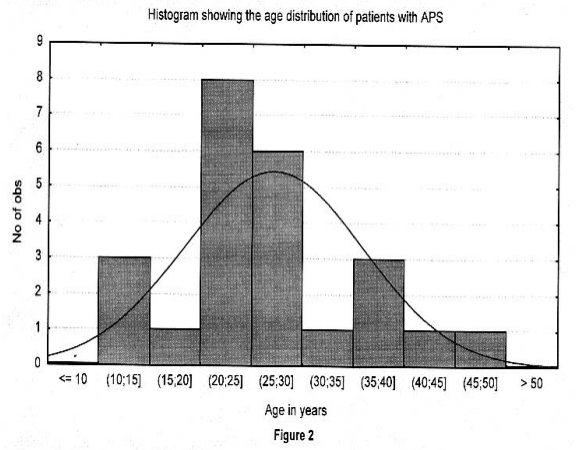

Figure 2

Table 1: Clinical resentation

Clinical Event	No.	Percent
Thrombosis	13	54.16
Abortion	2	8.33
Abortion and Thrombosis	2	8.33
Bleeding	2	8.33
Anemia	2	8.33

Table 2 : Sites of thrombotic e isodes

Site	No.	Percent
Lower limb PVT	1 5	62.5
Portal veins	2	833
Cerebral arteries	2	833
Rural sinuses	1	4.16

Table 3 :Other clinical features

Event	No	Percent
Bleeding	3	125
History of Abortion	10/13	76.9
Fits	3	125
Family history	2	833

Table 4 :Abortions

Timing	No.	%
Prefetal	16	43.24
Fetal	21	56.75
Total	37	100

Table 5 : Laborato findings

Parameter	NO	Percent
Anemia(HU<100g/L)	8	33.33
WBC<4x10^9/L	3	125
Platelet<100x10^9/L	5	20.8
ESR>30rnm/hour	11	45.83
P.7> 13seconds	7	29.16
P.T.T>40seconds	13	54.16
KCT&KCT Abnormal index	14/23	60.86
aCT>l0U/ml	15/19	78.94
ANA positive	9	37.5
Urinalysis abnormal	4	16.66

Table 6: Treatment

Drug	No	Percent
Anticoagulants	14	56.5
Corticosteroid	14	56.5
Aspirin	16	66.66
Immunosuppressive ssive	6	26.08

Table 7:Fate

Alive	22	95.65%
Dead	1	4.35%
Total	23	100%

Discussion:

Our small study collected 24 patients who fulfilled the criteria of APS showed that 75% of the study patient were female and the age of presentation in majority of the case was 21-30 years In comparison with the literature it seems that our community habits of earlier age of girl marriage makes the female at an earlier age of presentation and to be in the scope of the problem. Thirteen (54.16%) of our patients presented with thrombotic episodes but if we add the other 2patients who presented with abortion and thrombosis, the patient who had with thrombotic episodes rise to 62.5% which is not much different from the literature (1,4,7). Also 46.66% of our patient who had thrombosis had more than one attack of thrombosis which is also not much different from the literature (4,7,10) .

Abortion occurred in 10 of 13 married premenapausal ladies included in our study, five (50%) of those ladies had more than three abortions; this high percentage of abortions is partly attributed to our patient selection but still we think that APS is an important risk factor of recurrent abortions which any treating physician should consider. Bleeding (8.3%) was rare as in the literature (3). Anemia occurred in8(33.33%) of our study patient acquired immune hemolytic anemia in 4 patient (16.66%) which is in the range of values mentioned in the literature (14-23%)(3), thrombocytopenia occurred in 5 patient (20.8%),other laboratory values showed that P.T is prolonged in 7(29.16%) patient and P.T.T in 13(54.16%) ANA was positive in 9 patient (37.5%) two of them fulfilled the criteria of SLE (1,7,11).

We treated patients with thrombosis with anticoagulation (Heparin then Warfarin) with a target INR of 3-4 , and most of them we considered anticoagulation indefinitely As for pregnant ladies we used Heparin & Aspirin Corticosteroids used for patients in whom disease activity was not controlled by the above measures or patients with bleeding or hemolytic anemia, immunosuppressive(Azathioprine or cyclophosphamide), were used for patients with catastrophic APS , or disease uncontrolled by corticosteroids.

Conclusions & Recommendations:

We think that our study is too small and early to make important conclusions about the features of the disease and its incidence in our community. We are going to extend our study including new patient recruitment and longer follow up.

Our aim was to highlight a disease with diverse clinical presentations in hematology, neurology, general medicine and gynecology that need to screen for in the proper settings,and to present our experience in treating these patients.

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