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Antiphospholipid Antibodies in Egyptian Patients with Chronic Renal Failure

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The objectives of present research was to detect the incidence of antiphospholipid antibodies among Egyptian patients with chronic renal failure and its relation to their clinical manifestation and vascular access thrombosis. This study including 80 patients with chronic renal disease divided into two groups. Group A, forty patients with impaired renal function and group B, forty patients in chronic renal failure on hemodialysis. In addition to 10 age and sex matched subjects as a control group. All of them were subjected to clinical examination and laboratory investigation including antiphospholipid antibodies. Lupus anticoagulant was present in 21.25%, aCL IgM in 18.75% while aCL IgG in 11.25% of whole chronic renal disease patients. There was higher incidence of antiphospholipid antibodies in-group B end stage renal failure on hemodialysis (28/40(70%)) compared to group A of renal impairment (25/40(62.5%)). Also there was insignificant relationship between antiphospholipid antibodies and age, kidney function or liver function tests. There is increase of antiphospholipid antibodies among patients with chronic renal failure with great liability for thrombosis of vascular access. Also patients with positive LA have a great possibility to be hypertensive. HCV infection in hemodialysis group may be the cause of increased incidence of antibodies. Antiphospholipid antibody profile should be done for patients with recurrent thrombosis of vascular shunt, as it is the main cause of hospitalization of dialysis patients.

Key words: Renal failure, antiphospholipid, anticardiolipin antibodies, LA

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INTRODUCTION

Antiphospholipid syndrome (APS) is a non-inflammatory autoimmune disease. Recurrent thrombosis with an adverse pregnancy history and the presence of antiphospholipid antibodies (aPL) defines this syndrome (Maria and Graham, 2001). It is a disorder of hypercoagulability in association with circulating antiphospholipid antibodies directed against epitopes on oxidized phospholipids complexed with beta 2-glycoprotein-1, or against the glycoprotein itself (Vaidya *et al*., 2000). The most detected subgroups of aPL are lupus anticoagulant antibodies, anticardiolipin antibodies and B2 glycoprotien-1 antibodies. Lupus anticoagulant antibodies are more specific for the antiphospholipid syndrome, whereas anticardiolipin are more sensitive (De Groot *et al*., 1996).

Naito *et al*. (1999) found that antiphospholipid antibodies were report to occur in 13% of patients with chronic renal failure. In Egypt, the prevalence of treated end stage kidney disease in 1974 was less than 10 per million of the general population (Barsoum *et al*., 1974). In 1996 the prevalence recorded was about 165 per million (Barsoum, 1996). By the year 2000, the prevalence of dialysis patients become 311 per million (Egyptian Renal Registry, 2000). There is a significantly higher prevalence of aPL antibodies in patients with end stage kidney disease compared with general population, exceeding 30% in some studies (Brunet *et al*., 1995). These antibodies cross-react with phospholipids contains proteins, including protein C and S rendering them functionally deficient. Generation of these autoantibodies may be linked to accelerate apoptosis is an association between hepatitis C infection and anticardiolipin antibodies (aCL) (Gumber and Chopra, 1995).

Anticardiolipin antibodies and/or lupus anticoagulant may be associated with a number of viral infections; including hepatitis C virus (Imad and Azudi, 2002). Several studies reported that 13-20% of the hepatitis C virus (HCV) patients had significant titers of CL antibodies (Matsuda *et al*., 1995; Levy *et al*., 1997). But it remains unknown whether a CL antibodies are an epiphenomenon of HCV infection or whether cross-reactivity exists between aCL antibodies and any HCV antigen (Ordi-Ros *et al*., 2000).

Aim of the study was to detect the incidence of antiphospholipid antibodies in Egyptian patients with chronic kidney disease, also the relationship between the vascular access thrombosis and antiphospholipid antibodies and its association with hepatitis C infection among dialyzed patients.

MATERIALS AND METHODS

This study was conducted on 80 patients with chronic renal disease, were selected from Hemodialysis Unit in Internal Medicine Department of EL-Zahraa Hospital, from June 2002 to June 2004 and were divided into 2 groups: -

Group A: forty patients with impaired renal function. They were 22 males (55%) with mean age 56.7±18.13 years and 18 females (45%) with mean age 54.6±10.14 years.

Group B: forty patients with end stage renal failure undergoing hemodialysis. They were 19 males (47.5%) with mean age 50.9±12.5 and 21 females (52.5%) with mean age 54.86±9.0 years. The duration of dialysis was 2.90±2.00 years in males and 4.00±1.90 years in females.

In addition to ten apparently healthy individual (5 males and 5 females). Their mean age was 55.3±10.4 years as a control group.

About 10 mL of venous blood sample were taken from each subject participating in the study and divided into aliquots: The 1st aliquot about 2 mL were taken on EDTA for the determination of blood picture. The 2nd aliquot 1.6 mL put in a tube contains 0.4 mL citrate for the determination of ESR. The 3rd aliquot 1.8 mL of blood were put in a tube contain citrate for the determination of lupus anticoagulant antibody. The 4th aliquot were left to clot and separated by centrifugation and stored at -20°C for determination of kidney and liver function tests and antiphospholipid antibodies.

All patients were subjected to the following:

- Full clinical history and clinical examination.
- Laboratory investigations, which included:
- Full blood picture (Groner and Epstein, 1982), on Coulter Counter T890 (Coulter Counter, Harpenden, UK).
- Erythrocyte sedimentation rate by Westergreen's method (Mosely and Bull, 1981).

Kidney function test: A timed urine samples were taken from each subject participating in the study to perform creatinine clearance. A venous blood sample (about 3 mL) was also collected during the period of urine collection. Serum and urine creatinine were determined by alkaline picrate method (Höuöt, 1985). The standard formula for calculation of clearance was used (Payne, 1986). Colorimetric techniques were used for the determination of serum urea by Berthelot`s reaction (Patton and Crouch, 1977).

Liver function tests: Serum aspartate (AST) and alanine (ALT) aminotransaminases were determined

calorimetrically using Reitman and Frankle (1957) techniques. Serum alkaline phosphatase (ALP) was determined by the method described by Kind and King (1954).

Antiphospholipid antibodies

Anticardiolipin (aCL) antibodies: The anticardiolipin antibodies IgM and IgG was estimated using an indirect solid phase enzyme immunometric (ELIZA) assay, supplied by Orgentec Diagnostic (Carl-Zeiss-Strabe 49, Germany). Anticardiolipin results were expressed as GPL (IgG international antiphospholipid standard) or MPL (IgM antiphospholipid standard) U mL^{-1}. The upper limit of normal was 11 MPL units mL^{-1} for IgM and 23 GPL units mL^{-1} for IgG-aCL (Triplett, 1992).

Lupus anticoagulant antibody (LA antibody): Determination by activated Partial Thromboplastin Time (APTT). The kit was supplied from Biopool International (6025, Nicolle Street, Venture, USA). Typically normal results are approximately 28-36 sec (Hillmen and Lusher, 1982).

Others: ECG, echocardiography and brain CT scan for some patients.

Statistical analysis: The data were presented as mean±SD. Student's t test; Chi square test and Spearman correlation coefficient were used. ANOVA were used. The data were analyzed using Microsoft Excel 2000.

RESULTS

This study was conducted on 80 patients with chronic renal disease divided into two groups: -

Results of Table 1 showed that lupus anticoagulant was present in 21.25%, aCL IgM in 18.75% while aCL IgG in 11.25% of whole chronic renal disease patients. There was higher incidence of antiphospholipid antibodies in-group B end stage renal failure on haemodialysis (28/40(70%)) compared to group A of renal impairment (25/40(62.5%)).

Table 1: Incidence of antiphospolipid antibodies in 80 patients with chronic kidney disease, 40 patients with impaired kidney function (group A) and 40 patients with end stage kidney disease on hemodialysis (group B)

	Groups		
Auto antibodies	Whole patients No. = 80	Renal impairment patients No. = 40	Haemodialysis patients No.=40
Lupus anticoagulant (LA)	17(21.25%)	9(22.5%)	8(20%)
aCL IgG antibodies	9(11.25%)	4(10%)	5(12.5%)
aCL IgM antibodies	15(18.75%)	7(17.5%)	8(20%)
aCL IgG and LA antibodies	1(1.25%)	-	1(2.5%)
aCL IgM and LA antibodies	8(10%)	3(7.5%)	5(12.5%)
aCL IgG and IgM	3(3.75%)	2(5%)	1(2.5%)
no antibodies	27(33.75%)	15(37.5%)	12(30%)

Table 2: Clinical feature in 40 patients with impaired kidney function versus 40 patients with end stage kidney disease

	Groups	
Clinical feature	Renal impairment patients	Haemodialysis patients
Hypertension	24(60%)	35(87.8%)
Hepatitis C infection	6(15%)	40(100%)
Ischemic heart disease	14(35%)	6(15%)
Diabetes	20(50%)	5(12.5%)
Thrombotic events	10(25%)	4(10%)
Thrombosis of vascular access	-	3(7.5%)

Table 2 showed some clinical features in 40 patients with impaired renal function versus 40 patients (group A) with end stage renal failure on haemodialysis (group B). There was higher incidence of hypertension, hepatitis C infection and thrombosis of vascular access in-group B compared with group A patients. Also, there was higher incidence of ischemic heart disease, diabetes and thrombotic events among group A compared to group B patients.

There was higher incidence of antiphospholipid antibodies among patients with hypertension, then diabetes, then thrombotic events then ischemic heart disease and then hepatitis C infection (Table 3).

There was higher incidence of antiphospholipid antibodies among patients with hepatitis C infection, then hypertension, then ischemic heart disease, then thrombosis of vascular access and thrombotic events (Table 4).

Table 3: Antiphospholipid antibodies in relation to clinical feature among 40 patients with impaired kidney function (group A)

	Clinical features				
Antibodies	Hypertension	Hepatitis C	Ischemic heart disease	Diabetes	Thrombotic events
Lupus anticoagulant	11(45.8%)	1(16.6%)	5(25%)	6(30%)	5(50%)
aCL IgG	4(16.6%)		1(7.1%)	3(15%)	
aCL IgM	8(33.3%)	3(50%)	2(14.2%)	7(35%)	5(50%)
aCL IgG and LA					
aCL IgM and LA	3(12.5 %)	1(16.6%)			2(20%)
aCL IgG and IgM	1(4.1%)				

Table 4: Antiphospholipid antibodies in relation to clinical feature among 40 patients with chronic kidney failure on regular hemodialysis (group B)

	Clinical feature					
Antibodies	Hypertension	Hepatitis C	Ischemic heart disease	Diabetes	Thrombotic events	Thrombosis of vascular access
Lupus anticoagulant	12(34.2%)	14(35%)	4(66.6%)	1(20%)	1(25%)	
aCL IgG	5(14.24%)	8(20%)		1(20%)		1(33.3%)
aCL IgM	14(40%)	14(35%)	4(66.6%)	1(20%)	1(25%)	2(66.6%)
aCL IgG and LA	1(2.8%)	1(2.5%)				
aCL IgM and LA	5(14.2%)	5(12.5%)	2(33.3%)		1(25%)	
aCL IgG and IgM	1(2.8%)	1(2.5%)				

Table 5: The different laboratory parameters among different patient groups. (Mean±SD)

	Groups			
Parameters	Impaired kidney function	Haemodialysis patients	Normal control	p-value*
aCL IgG (U mL^{-1})	20.03±27.16	23.25±29.30	19.7±1.5	<0.001
aCL IgM (U mL^{-1})	13.60±14.88	15.43±14.34	8.5±1.7	<0.001
LA antibody (seconds)	32.63±3.18	33.47±3.6	31.1±2.3	<0.001
Serum creatinine (mg dL^{-1})	3.62±2.31	9.33 ±2.25	0.91±0.16	<0.05
Serum urea (mg dL^{-1})	118.25±55.85	157.0±87.36	38.40±4.07	<0.05
AST (U L^{-1})	33.57±18.17	44.60±36.25	12.5±8.40	<0.001
ALT (U L^{-1})	34.37±17.43	39.30±20.70	15.4±9.3	<0.001
ALP (U L^{-1})	239.30±89.19	260.05± 110.28	210.8±45.91	<0.001
RBCs (million/C mm)	3.05±0.72	2.81±0.74	4.11± 0.79	<0.05
WBCs (Thousand/C mm)	8.81±3.60	7.59±3.07	8.9±2.4	<0.001
Hb (g%)	9.04±2.10	8.16±1.83	12.2±1.6	>0.05
Platelets (Thousand/C mm)	230.97±83. 06	219.75±90.4	257.5±84.5	<0.001

* $p<0.05$: Non significant, $p<0.001$: Highly significant, $p>0.05$: Significant

Table 5 showed the different laboratory parameters among different patient groups. There was a highly significant increase in aCL, IgG and IgM antibodies, lupus anticoagulant, aspartate and alanine aminotransferases and alkaline phosphatase and a significant increase in serum urea and serum creatinine in-patient groups compared with the control group. A highly significant decrease in white blood cell count (WBCs), platelets and a significant decrease in red blood cell count (RBCs) and a non-significant decrease in hemoglobin in the 2 patient groups compared to control group were found.

DISCUSSION

Chronic kidney failure is defined as the irreversible, substantial and usually long standing loss of kidney function causing ill health, while end stage kidney failure (ESKF) is the degree of chronic kidney failure that without replacement treatment would result in death (El-Nahas and Winealrs, 1999).

Antiphospholipid syndrome (APS) is a non-inflammatory autoimmune disease. Recurrent thrombosis with an adverse pregnancy history and the presence of antiphospholipid antibodies (aPL) defines this syndrome (Maria and Graham, 2001). Antiphospholipid syndrome may be primary or secondary type associated with connective tissue disorders, giant cell arteritis or Wagener's granulomatosis (Martin *et al*., 2001). With no much clinical difference between the two types (Imad and Azudi, 2002).

However anticardiolipin antibodies and/or lupus anticoagulant may be associated with several situations other than antiphospholipid syndrome. It may be associated with a number of viral infections including hepatitis C virus, human immune deficiency virus, cytomegalovirus, varicella, Epstein-Barr virus, adenovirus and provirus β. In many instances, the presence of these antibodies may associate with thrombosis (Imad and Azudi, 2002). Also, in patients with stroke studies by Luong *et al*. (2001) over 7 years period, there was good percentage of positive test of antiphospholipid antibodies with different titers. Even in normal subject, positive cases may be present with attack of chest infection or rheumatic fever.

Naito *et al*. (1999) found that antiphospholipid antibodies were reported to occur in 13% of patients with chronic renal failure with high incidence of hemodialysis access thrombosis. Also, Viadye *et al*. (2000) found ninety-three patients (19%) of their studied group have high titer of anticardiolipin antibodies. In 2002 studied 169 end stage renal disease patients for anticardiolipin, 28 patients were positive for antibody and 24 of them had clotting disorder including cerebrovascular thrombosis, thrombosis of vascular access shunts or repeated abortion (Vaidya *et al*., 2002).

In the present study on 80 patients with chronic kidney disease, lupus anticoagulant antibodies were found in 21.25%, while aCL IgM in 18.78% and aCL IgG in 11.25%. So the frequency of anticardiolipin antibodies was more or less similar to the results reported by Vaidya *et al*., (2000, 2002). But as regard the clotting

disorders we found it in 17 patients only (13.2%); ten of them had antiphospholipid antibodies.

When we classified the patients into two groups, we found the incidence of aCL IgM in 20%, LA in 20% and aCL IgG in 12.5% in 40 patients with chronic renal failure on regular haemodialysis. While aCL IgM in 17.5%, LA in 22.5% and aCL IgG in 10% in 40 patients with impaired renal function. So there was high incidence of antiphospholipid antibodies among chronic kidney failure on regular haemodialysis group 28/40 (70%) than those with impaired renal function 25/40 (62.5%), but the difference was statistically insignificant. These results can explained as all our hemodialysis patients (100%) were HCV infected in contrast to only 6 (15%) in renal impairment group. Also the oxidative stress occurred during dialysis may play a role (Joseph *et al*., 2001).

In agreement with (Fabrizi *et al*., 1999) we found no correlation between antiphospholipid antibodies and age, kidney function tests, liver function tests or blood picture results. In addition Fabrizi *et al*. (1999) found no correlation to duration of dialysis, type of dialysis membrane or hemorrhagic events.

In the present study we found clotting disorders in 17 patients, 10 (58.8%) of them had antiphospholipid antibodies. Also we found that patients with aCL IgM and IgG antibodies have great liability for shunt thrombosis. These results in agreement with that obtained by Brunet *et al*. (1995) and Fabrizi *et al*. (1999). This can be explained as the antiphospholipid antibodies cross react with phospholipids containing protein including protein C and S rendering them functionally deficient. Generation of these antibodies may be linked to accelerate apoptosis in ESKD. Also the reduced antithrombin III activity related to uremic toxins and inadequate release of tissue plasminogen activator in uremia can prevent lyses of formed clot (Sloand, 2000).

In this study, the incidence of hypertension in whole studied group was 59 patients 23 of them had LA antibodies, 9 had aCL IgG and 22 had aCL IgM antibodies. This result was in agreement with that obtained with Nochy *et al*. (1999) and Rolino *et al*. (2003). Also we found that patients with LA positive antibody tend to be hypertensive.

Herbert *et al*. (1997) postulated that the increased blood pressure might impair kidney function by inducing arteriolar nephrosclerosis. Also hypertension induced tissue injury may involve stretch induced tissue fibrosis, an up regulation of intracellular adhesion molecules that result in renal infiltration of lymphocyte and macrophage. When hypertension super-imposed on intrinsic renal disease the resulting arteriolar nephrosclerosis add to renal disease progression

CONCLUSIONS AND RECOMMENDATION

There is increase of antiphospholipid antibodies among patients with chronic renal failure with great liability for thrombosis of vascular access. Also patients with positive LA have a great possibility to be hypertensive. HCV infection in hemodialysis group may be the cause of increased incidence of antibodies. More investigations should be directed to patients with end stage renal disease to detect cases of antiphospholipid syndrome presented by kidney disease. Also antiphospholipid antibody profile should be done for patients with recurrent thrombosis of vascular shunt, as it is the main cause of hospitalization of dialysis patients.

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