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PREVALENCE OF ANTI CARDIOLIPIN ANTIBODIES IN PATIENTS WITH SUSPECTED ANTI PHOSPOLIPID SYNDROME

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ABSTRACT
Aim: To estimate the prevalence (overall and the individual by clinical event type) of anti cardiolipin antibody (IgG, IgM positivity) in patients with suspected anti phospolipid syndrome. **Methodology:** 572 consecutive patients referred for evaluation of suspected antiphospolipid syndrome were screened for anti cardiolipin antibodies (IgG and IgM) by ELISA. Correlation between the type of antibody and the clinical events was analyzed. **Results:** Of the 109 patients referred for fetal losses 21 (19%) were positive for anti cardiolipin anti bodies. Of the total 153 cases referred for arterial thrombosis, 20 (19%) were positive for anticardiolipin and of the 147 cases with venous thrombosis 7 (4%) were positive for anti cardiolipin antibodies. Out of the 48 cases with positivity 33 had IgM positivity, 20 had IgG positivity and 5 had both. **Conclusion:** All patients presenting with recurrent fetal losses and thromboembolic phenomena should be screened for antiphospolipid antibodies.

KEYWORDS: Antiphosolipid syndrome, recurrent fetal loss, anticardiolipin antibody, venous thrombosis, arterial thrombosis.

INTRODUCTION
Anti phospolipid syndrome (APS) is a hypercoagulable state characterized by the presence of auto antibodies called Anti phospolipid antibodies (APLs). APS can occur as an isolated diagnosis, or it can be associated with other connective tissue disorders like systemic lupus erythematosus (SLE) or another rheumatic disease. 40% of patients with SLE and 20 % with RA have aPL positivity.[1,2] Antiphospholipid antibodies (aPLs) are a family of autoantibodies directed against phospholipid-binding plasma proteins, most commonly β_2-glycoprotein I. The auto antibodies include anticardiolipin antibodies (aCL), anti β_2 Glycoprotein I as measured by solid phase assay and Lupus anticoagulant as measured by coagulation assay-inhibitor of phospolipid dependent clotting. Transient aPL, can occur in normal blood donors[1,3] or following infections or drugs.[4] But persistent positivity and moderate to high titres of aCL, β_2GPI Ab or a positive anti coagulant occur in less than 1% of the population. The prevalence of positive Abs increases with age.

The clinical manifestations of APS can be protean. It may remain asymptomatic, cause recurrent fetal losses, arterial and venous thrombosis. Sometimes a severe form of APS called catastrophic APS characterized by multiple thromboses of medium and small arteries occurs. Pregnancy losses typically occur after 10 weeks' gestation (fetal loss), but earlier losses also occur though chromosomal and genetic defects are commonly responsible for earlier losses. Slowing of fetal growth, reduction in amniotic fluid volume, severe preeclampsia and HELLP syndrome can also be the manifestations of APS. The primary predictor of adverse pregnancy outcome after 12 weeks gestation in aPL associated pregnancies was Lupus anti coagulant others being prior thrombosis and SLE.[5]

Stroke is the most common presentation of arterial thrombosis; deep vein thrombosis is the most common venous manifestation of APS.

APS account for 6% of pregnancy morbidity[6], 20% of recurrent fetal losses[7], 14% of stroke, 17% of young stroke[8], 11% of myocardial infarction[6], 10% of deep vein thrombosis and 14% of recurrent venous thromboembolism.[9]

Diagnosis should be made in the presence of characteristic clinical manifestations and persistently positive aPLs (measured at least 12 weeks apart). The diagnosis of APS requires a positive lupus anticoagulant test or a moderate- to high-titer anticardiolipin or anti-β2GPI IgG or IgM test in patients with characteristic clinical manifestations. Diagnosis of APS is made according to the Sapporo classification revised in 2004.[10.11] Patients with negative lupus anticoagulant and

anticardiolipin tests should be tested for IgA anticardiolipin and IgG, IgM, or IgA anti-β2GPI when there is a high suspicion of APS.

Early identification APS as the cause for thromboembolic events and pregnancy morbidity and correct treatment can prevent future complications like life threatening thormboembolic events and fetal losses. The social and psychological impact of recurrent fetal losses can be huge in a country like India. Hence it is prudent that early identification of APS in such cases is highly essential. So this study was done to estimate the prevalence of anticardiolipin antibodies in suspected cases of Antiphospolipid syndrome.

METHODOLOGY

The study was a cross sectional observational study. 572 consecutive cases referred to Rheumatic Care Center, Chennai for suspected anti phospolipid syndrome were screened for anticardiolipin antibodies by ELISA technique. The anticardiolipins that were identified include isotypes IgG and IgM. Of these 109 were referred for evaluation of recurrent fetal losses. Remaining 463 patients were referred for evaluation of deep vein thrombosis, cerebro vascular accidents, cortical venous thrombosis, transient ischemic attacks, avascular necrosis and antiphospolipid syndrome secondary to connective tissue disorders like SLE. The overall and the individual prevalence of antiphospolipid antibodies were estimated. The results were analyzed using chi square test. Estimation of β2 glycoprotein and lupus anti coagulant was not done due to financial constraints.

RESULTS

The total number of cases were 572. Of these 109 were referred for evaluation of recurrent fetal losses. 153 were referred for arterial thrombosis, 147 for venous thrombosis and rest were referred for screening in other connective tissue disorders. Total number of cases positive for anticardiolipin antibodies was 48 (8.39%) **(Figure 1)**. Of these 21 patients had recurrent fetal losses. 20 had arterial thrombosis and 7 had venous thrombosis. Of the 109 patients referred for fetal losses 21 (19%) were positive for anti cardiolipin anti bodies. Of the total 153 cases referred for arterial thrombosis, 20 (19%) were positive for anticardiolipin and of the 147 cases with venous thrombosis 7 (4%) were positive for anti cardiolipin antibodies. **(Table 1. Figure 2).**

Out of the 21 patients with fetal losses and positivity, 11 had IgG positivity, 12 had IgM positivity and 2 had both. Similarly of the 20 patients with arterial events and positivity, 15 had IgM positivity 7had IgG positivity, 2 had both. Of the 7 patients with venous events, 2 had IgG positivity 6 had IgM positivity and 1had both. (**Table 2).** Out of the 48 cases with positivity 33 had IgM positivity, 20 had IgG positivity and 5 had both.(**Figure3).**
Eventhough there was an apparent increased percentage of IgM positivity the result was not statistically significant. Using Chi square test the p value was 0.39 (> 0.05 hence not significant) (**Table 2).**

Table 1: Overall prevalence and individual split up of positivity.

	Total number	Positivity
Total No. of Patients	572	48 (8.39)
Fetal loss	109	21 (19%)
Arterial Thrombosis	153	20 (13.1)
Venous thrombosis	147	7 (4%)

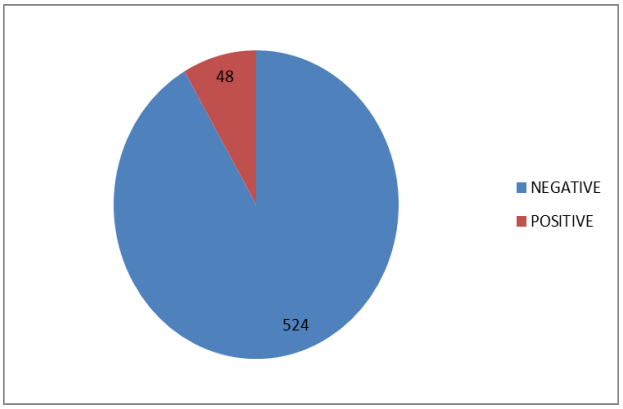

Figure 1: Showing overall prevalence of positivity.

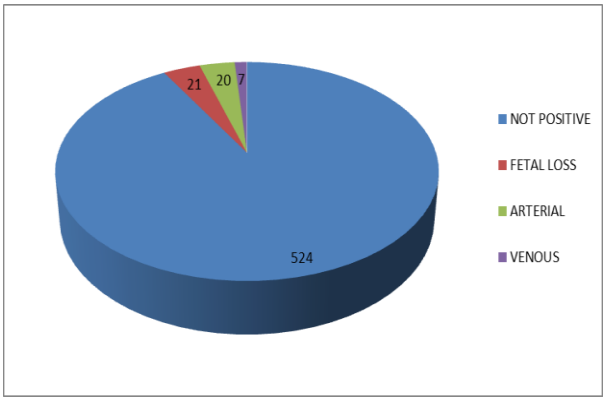

Figure 1: Showing overall and individual split up of positivity.

Table 2. Prevalence of positivity by individual isotype.

Event	IgM	IgG	Both	Total	p value 0.39 > 0.05 (not significant)
Fetal loss	12	11	2	21	
Arterial	15	7	2	20	
Venous	6	2	1	7	
Total	33	20	5	48	

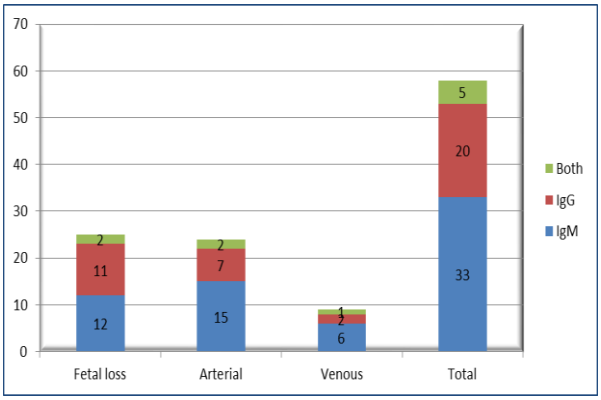

Figure 3: Prevalence of positivity by individual isotype.

DISCUSSION

APS is a hypercoagulable state characterized by the presence of a thrombotic event and aPLs including anticardiolipin, β2 glycoprotein inhibitor, and lupus anticoagulant.

In the present study the prevalence of anticardiolipin antibodies was identified in the patients referred for evaluation of suspected APS.

Of the total 572 patients, the referral split up was 109 for recurrent fetal losses, 153 for arterial events, 147 were referred for venous thrombosis and the rest were referred for screening of APS in other CTDs. Total no of positive results was 48 (8.39%). Of these 21 had recurrent fetal losses, 20 had arterial thrombosis and 7 had venous thrombosis. Of the 109 patients referred for recurrent fetal losses 19% (21) were positive for aCL antibodies. This matches standard estimates published in previous studies.[7]

The majority of arterial events for which the patients were referred for included cerebro vascular accidents (including young stroke), transient ischaemic attack, myocardial infarction. In this subgroup the percentage of positivity was 19% (20). This too matches standard estimates published in previous studies.[6,8]

Of the 21 patients with fetal losses and positivity, 11 had IgG positivity, 12 had IgM positivity and 2 had both. Similarly of the 20 patients with arterial events and positivity, 15 had IgM positivity 7had IgG positivity, 2 had both. Of the 7 patients with venous events, 2 had IgG positivity 6 had IgM positivity and 1had both. There was an apparent increase in the percentage of IgM positivity but the result was not statistically significant. Using Chi square test the p value was 0.39 (> 0.05). This is in line with previous published studies like Domingues V et al[12] where there was no association with IgM. But here all were SLE patients unlike our study population which consist of a mixed group of patients with suspected APS.

Again in this study the combination of isotypes did not increase the risk of clinical events. Only triple association (aCL, β2 glycoprotein Abs and Lupus Anticoagulant) increases the risk of thrombosis as proved in various previously published studies.[13]

The limitation of our study is that lupus anti coagulant which is a more specific test for thrombosis and correlates better with aPL related clinical events was not done due to cost constraints. The predictive power of aCL is due to its association with LAC which is the strongest predictor of pregnancy loss as shown in PROMISS ZxE study.[14] Other factors that predict adverse pregnancy outcomes include prior thrombosis, SLE, prior late pregnancy losses independent of APL profile.

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