Indications and Outcome of Anti-phospholipid Syndrome Testing in an Obstetric Population at Sabah Women & Children Hospital, Kota Kinabalu, Sabah, Borneo Malaysia

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SUMMARY

Aim: We audited indications and outcomes of antiphospholipid syndrome (APS) screening in the pregnant population at our centre. Method: Prospective and observational. All APS test results returned were audited for validity of indication and subsequent outcome. Result: 24 of a total of 146 (16%) of requests for the antiphospholipid antibodies and lupus anticoagulant were not indicated. Two positive results returned for a total of 116 "indicated" requests (1.7%). Conclusion: There needs to be increased awareness among obstetricians on the indications for screening for antiphospholipid syndrome (APS). The prevalence of antiphospholipid syndrome with obstetric manefestations in the study population is lower than rates published in the literature.

KEY WORDS:
Antiphospholipid antibody, Antiphospholipid syndrome, Intrauterine death, Intrauterine growth restriction, Pre-Eclampsia, recurrent miscarriages

INTRODUCTION

The antiphospholipid syndrome (APS) is a systemic disorder characterized by either vascular thrombosis or pregnancy morbidities such as recurrent miscarriages, intrauterine fetal demise (IUD), severe pre-eclampsia and intrauterine growth restriction[1,2,3]. Presence of the anticardiolipin antibody (ACL) or lupus anticoagulant (LA) in the setting clearly defined clinical manifestations confirms the diagnosis of APS[1]. As is with most autoimmune disorders, APS is a disease in evolution. Strict criteria (Sapporo criteria/consensus) has been established to maintain the sensitivity of diagnostic testing[1]. The diagnosis of APS requires, as a prerequisite, an index of suspicion by physicians or obstetricians and sound awareness of its diagnostic criteria. The apparent prevalence of APS relies on the tenet that all cases that fulfill the criteria are screened. All prevalence papers are a reflection of this awareness. The prevalence of APS in normal population has been quoted as 1-5%[4]. It has a higher prevalence (35%) among patients with systemic lupus erythomatosus (SLE)[2]. Since its inception in 1986 as the anticardiolipin syndrome[5], APS has currently evolved into an established disease entity. Treatment of APS based on its pathophysiological model is established[6,7]. We aimed to audit the awareness among physicians and obstetricians of the obstetric criteria for APS screening.

MATERIALS AND METHODS

Sabah Women & Children Hospital (SWACH) is a tertiary referral centre for the state of Sabah, Borneo Malaysia. The delivery rate the past 5 years averaged at 12,000 per year with a perinatal mortality rate of 13 per 1000 livebirths. APS screening is requested by any of the resident obstetricians or physicians. No local guidelines exist on the screening criteria at the time of the study. All APS study results are returned to the pre-pregnancy clinic for subsequent analysis. It is in this setting this audit was conducted. A dedicated nurse was assigned for data collection. It was the pre-audit hypothesis that requesting clinicians adhered to the international consensus of Sapporo when selecting cases for APS testing. The aim is to study the requesting patterns and outcome of APS testing at SWACH. We analysed the relevance of the APS tests requested against the Sapporo consensus. The Sapporo consensus statement of 1999 outlined that APS requires ONE of the following clinical manifestations AND fulfillment of ONE of the laboratory criteria for the diagnosis of APS.

Clinical criteria

1) Vascular thrombosis. One or more clinical episodes of arterial, venous, or small vessel thrombosis, occurring within any tissue or organ. With the exception of superficial venous thrombosis, thrombosis must be confirmed by imaging or Doppler studies or histopathology. For histopathologic 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 or
B) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation due to pre-eclampsia OR IUGR or
C) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to A, B, or C above.

Laboratory criteria

1. 1) Anticardiolipin antibodies. Anticardiolipin antibodies of immunoglobulin G and/or immunoglobulin M isotype in blood, present in medium or high titer (> 40 GPL or

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Table I: "Indicated" Screenings

Conditions	N (total)	N (positive test)
IUD	63	2 (3.17%)
Pre-Eclampsia	11	0
MISC	22	0
IUGR	5	0
DVT / CVA	6	0
SLE	2	0
THROMBOCYTOPENIA	2	0
TOTAL	111	2

IUD= intrauterine fetal demise, IUGR= intrauterine growth restriction, DVT= deep vein thrombosis, CVA= cerebrovascular accident, SLE= systemic lupus erythematosus, thrombocytopenia: investigated if values < 100,000/L.

Table II: "Non-Indicated" Screenings

Condition	N (total)	n (positive)
Abruptio placenta	5	0
Heart disease	1	0
IUGR with pre-eclampsia delivered beyond 34/40	3	0
Pre-embryonic miscarriages recurrent < 3 episodes	7	0
Stillbirths from intrapartum events	3	0
Late onset pre-eclampsia > 34/40	4	0
SLE "routine" with no prior clinical / lab criteria	12	0
TOTAL	35	0

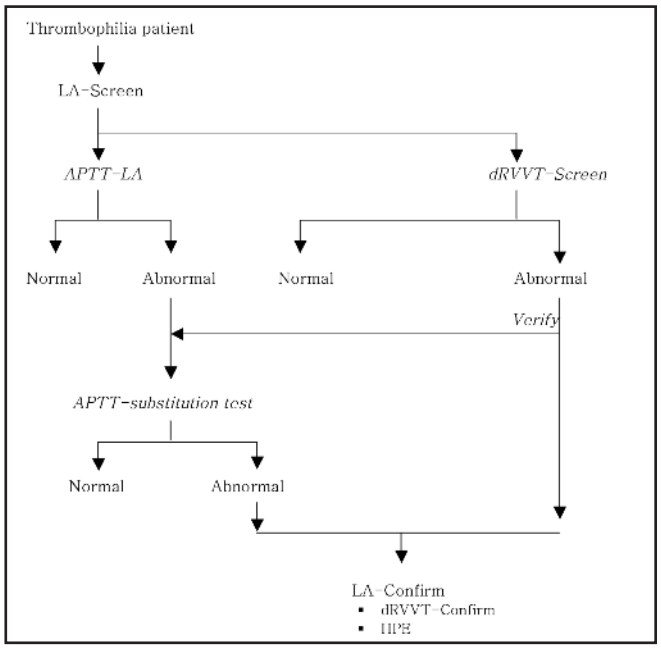

Fig. 1: Laboratory screening and confirmation of Lupus Anticoagulant.

MPL OR > 99th percentile: One GPL unit is equivalent to 1 µL/mL of IgG aCL immunoreactivity) on two or more occasions at least 6 weeks apart, measured by a standardized enzymelinked immunosorbent assay for β2-glycoprotein I–dependent anticardiolipin antibodies.

2) Lupus anticoagulant antibodies. Lupus anticoagulant present in plasma, on two or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis in the following steps:

A) Prolonged phospholipid-dependent coagulation demonstrated on a screening test (eg, activated partial thromboplastin time, kaolin clotting time, dilute Russell viper venom time, dilute prothrombin time, Textarin time)

B) Failure to correct the prolonged coagulation time on the screening test by mixing with normal, platelet-poor plasma

C) Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid

D) Exclusion of other coagulopathies (eg, factor VIII inhibitor) or heparin, as appropriate

Adapted.[1]

All APS test results returned from the 1st of January 2009 up to the 31st of December 2009 were analysed. Data collected include: (i) indication for testing and (ii) outcome of testing. A standard proforma was filled for all APS results returned. Data on indication was counterchecked against case notes. A test was considered positive if the APS screen was performed on two occasions. Requests meeting the Sapporo criteria are classified as "Indicated" and "Non-Indicated" if otherwise. APS screening is considered part of routine clinical services. Consent is implied as obtained when the patients agree to blood sampling for testing given the explanation. 10mls of venous blood is drawn by standard venepuncture.

Laboratory test methods

Blood samples from patients in this study were tested for anticardiolipin antibodies using the Immunoconcepts RELISA Cardiolipin IgG & IgM antibody test kit. Screening for LA was done with the following 3 tests: activated partial thromboplastin time (LA and mixing) and dilute Russel Viper Venom time (dRVVT), following which confirmatory tests was performed with the following: dRVVT and Hexagonal phase phosphatidyl ethanolamine test (HPE). Figure I illustrates the process for the laboratory diagnosis of LA.

This proposal was approved by the local hospital ethics committee and subsequently the Clinical Research Council via the National Medical Research Register of Malaysia. This research is assigned the NMRR registration of NMRR-08-1450-2498.

RESULTS

A total of 146 APS screenings were processed during the study period. Sapporo criteria for APS testing was met in 111 (76%) of these requests. Of these two tests were screen positive. The breakdown of indicated requests is given in Table I.

35 screens were returned negative for conditions where APS screening was not indicated. The indications are enumerated in Table II.

DISCUSSION

Inappropriate testing accounted for 24% of all screenings for APS. This could represent the degree of awareness among obstetricians on the criteria for APS screening. APS requires stringent criteria for diagnosis. Adherence to agreed criteria is vital to avoid false positives and maintain the sensitivity of the consensus. The long term medical and obstetric implications of false positive tests is significant with possible lifelong or gestation-long confusion and possible inappropriate treatment for unrealistic thrombotic or obstetric risks. All 35 non-indicated tests were negative. It is vital that APS screening be carried out only when defining criteria are met. The false sense of security of a falsely clinched diagnosis may lower the obstetricians or physicians guard to other colluding causes.

It will be evident from the criteria listed above1 that obstetric units would probably be over-screening in some categories and under-screening some in others. Based on observation and communications, the author has reason to believe that APS would probably be over-screened in cases of IUD (malformed fetus, hydrops fetalis) and first trimester (< 10 weeks) miscarriages. Under-screening would probably be prevalent in severe PET and/or IUGR requiring delivery prior to 34 weeks gestation, embryonic miscarriages (> 10 weeks after confirmation of viable and normal fetus) and thrombocytopenia with most women with low platelets clumped in either gestational thrombocytopenia or idiopathic thrombocytopenia diagnoses.

There were two positive APS screens. This would give an incidence of 1.7% of the 116 screen-indicated cases. This is not above the reported population rate of 1-5%. Studies have shown rates as high as 29% in a cohort with late pregnancy loss. The 2 positives were requested for intrauterine fetal demises giving an incidence of APS in IUD of 3.17%. It is probable that the prevalence of APS in the studied population is low. We recognize that the number of subject is small for conclusive statements but the sample size is not negligible in spite of it being a pilot observational.

It is plausible that the role of APS in obstetrics is over-emphasized. Most glaring is the pool of 63 women with IUDs. All but two were tested negative. However, requests were not streamlined. All IUDs were clumped together regardless of probable cause and APS screen ordered for all as per unit protocol. It was not ascertained if all indicated cases were screened. The Sapporo statement states APS screening is indicated when in-utero demise of normally formed fetus occurs beyond 10 weeks of gestation. More stringent criteria for APS testing in cases of IUD may obtain higher yield and reduce unnecessary testing and intervention.

Twenty two subjects in the cohort had 3 first trimester recurrent miscarriages. There was no APS positivity in this group. The prevalence of APS in recurrent 1st trimester (pre-embryonic) miscarriages is 10-20%[9]. One would expect approximately 4 positives in this sample group of 22 but again the numbers in this study is too small to conclude.

Despite being a prospective audit, only cases where the results are returned are considered for analysis. The number of cases where APS testing were ordered but no results were available in the notes was not ascertained.

Future audits should be based on the revised consensus criteria for the diagnosis of definite APS by Miyakis *et al*[10]. The Miyakis consensus maintains the Sapporo criteria for screening but suggested the following revisions: (i) once indicated testing should be performed 12 weeks apart, (ii) testing is best after due interval (12 weeks) from the clinical event, (iii) Sapporo 2a: one or more unexplained deaths of morphologically normal fetus beyond 10 weeks by ultrasound or direct examination, (iv) Sapporo 2c: 3 consecutive miscarriages < 10 weeks after confirmation of normal anatomy, hormonal states and parental chromosomes and (v) Lab: addition of anti-β2 Glycoprotein 1 essay as one of the testing for APS. These findings have prompted a move towards a local consensus on screening.

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