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LUPUS ANTICOAGULANTS: PATHOPHYSIOLOGY, CLINICAL AND LABORATORY ASSOCIATIONS: A REVIEW
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ABSTRACT

Objectives: **To put together salient clinical and laboratory manifestations and also to highlight the pathophysiology and principles of management of lupus anticoagulants syndrome.**
Data Sources: **Publications, original and review articles, conference abstracts searched mainly on PubMed indexed for Medline.**
Data extraction: **A systematic review to identify studies relating to lupus anticoagulants, clinical, laboratory, pathophysiology and management. Only data relevant to the objectives of the review were extracted.**
Data synthesis: **A detailed qualitative assessment was undertaken given the heterogeneity of study types making it not appropriate to pool results across studies.**
Conclusion: **It is demonstrated that lupus anticoagulants (LA) are associated with thrombotic events, recurrent foetal loss and female infertility and also occasionally with bleeding due to thrombocytopenia or hypoprothrombinaemia LA interferes with phospholipid dependent laboratory test of coagulation and the test are not corrected by addition of normal plasma. False positive antiphospholipid antibody test is noted frequently in patients. LA has been detected in all races and geographical regions in the world. The treatment involves use of corticosteroids, anticoagulants, immunoglobulins and occasionally cytotoxic drugs and plasmapheresis long term prophylaxis and follow up of patients with IgG antiphospholipid antibodies are recommended. Screening for LA considered in patients with unexplained; thrombotic events, foetal loss and bleeding.**

INTRODUCTION

In 1952, Conley and Hartman identified a circulating anticoagulant and because of its frequency in patients with Systemic Lupus Erythromatosus (SLE), Feinstein and Rappaport coined the term Lupus anticoagulant (LA)(1). However the majority of the patients do not have underlying SLE. LA is associated with thrombosis but occasionally with bleeding(2).

LAs are immunoglobulins IgG, IgM, IgA or mixture and are a form of antiphospholipids. Together with anticardiolipin (a-CL) antibodies they are the commonest encountered antiphospholipids (APA)(3).

The SCC sub committee for standardization of lupus anticoagulant in 1995 restated criteria for its laboratory diagnosis as follows(4):

(i) Prolongation of at least one phospholipid dependent clotting test.
(ii) Evidence of inhibitory activity demonstrated by mixing studies.
(iii) Evidence that inhibitory activity is dependent on phospholipid and
(iv) Exclusion of other coagulopathies that give similar laboratory results or may occur concurrently with LA.

LA have marked heterogeneity and like other-Antiphospholipid Antibodies (APA) may present with involvement of virtually every organ system of the body(3). However patients commonly with systemic lupus erythematosus (SLE) or other autoimmune disorders, those with neoplasms on therapy with drugs and some without apparently underlying disease have also been found to have LA(4).

Case reports and analyses of large series have shown that the syndrome is associated with increased risk of thrombotic events and Pierangeli *et al.* have experimentally induced thrombosis in a mouse model by injecting immunoglobulins IgG, IgM and IgA purified from patients with the antiphospholipid syndrome(5).

The manifestations are protean and can masquerade as exemplified by Gasperi *et al* (6). It is therefore compelling to keep reporting, and reviewing information on LA not to risk being caught off guard by uncharacteristic presentations.

This review describes the clinical associations and also provides a framework for the management of the patients with LA syndrome.

Incidence: The frequency in the normal population has varied but approximately 3.6% are LA

positive(7). This could be due to infections or could be drug induced. High prevalence is seen in disease conditions such as peripheral vascular disease recurrent foetal losses and acquired thrombotic episodes. Other disease conditions which show high prevalence include; pulmonary hypertension, heparin related thrombocytopaenia, cerebral vascular disease in young patients, many autoimmune disorders including rheumatoid arthritis, lymphoploriferative diseases, drug reactions, infections, cardiovascular disease and malignancies. For instance unexplained infertility compared with ovulatory infertility have 20.5% versus 3.3% in a study by Kim *et al.* and more in SLE than non-SLE disorders with an average frequency of 34% in patients with SLE(8).

Sex: Primary LA occurs equally in both males and females. However, the secondary form is more frequent in females. Recurrent foetal loss, placental vascular pathologies, post partum syndrome, chorea gravidarum, pre-eclamptic toxaemia and infertility primarily affect females(9). Only one of the six adult cases the author has recorded over the last three years is male (unpublished data).

Age*:* The majority are between 25 and 40 years old, however there are reports of paediatric age groups and those older than 50 years. Gattorno *et al.* have demonstrated LA in paediatric patients while children with thrombosis and even foetal renal vein thrombosis, hydrops fetalis and maternal LA have been reported(10,11). The author's unpublished data show peak age between 25 and 32 years.

Geographical distribution: LA have been reported from most geographical regions of the world. The author has published a case of LA from Kenya in East Africa and there are several reports from Europe, Asia, America and Australia(12,13).

Pathophysiology:

The immunoglobulins are hetelogeneous the pathophysiology multifaceted and are species specific. LA is known to act on the phospholipid dependent phases of coagulation cascade; but other mechanisms are likely to be involved as well. The following are some of the pathophysiological mechanisms believed to be involved.

(i) Prothrombin: LA is observed to inhibit generation of prothrombin activator complex which is formed by the interaction of activated factor X, factor V, and platelet phospholipid in the presence of calcium. Several reports show that LA IgG^2 inhibit more effectively and consistently the Xa Va phospholipid complex catalysed activation of human prothrobin(14).

(ii) Beta-2 glycoprotein: Beta 2 glycoprotein functions as a physiologic anticoagulant inhibiting the contact phase of coagulation as well as ADP induced platelet aggregation. LA APA could be inhibiting the anticoagulant effect of beta 2 factor Xa. This results in increased generation of Xa which could predispose the thrombosis(14,15).

(iii) Vascular: Studies have reported sera or IgGs from patients with LA inducing factor activity in cultured endothelial cells. Brandt demonstrated that the expression of tissue factor on endothelial cells by isolated IgG from LA positive patients correlated with a clinical history of thrombosis(15) Carreras and colleagues were the first to find certain APA positive patients plasma were able to inhibit prostacyclin-2 (PGI-2) production(16). PGI-2 is a potent vasodilator and inhibitor of platelet aggregation hence the balance of PGI-2 and thromboxaemia A_2 (TXA_2) a platelet aggregation promoter would be altered in favour of a prethrombotic state.

(iv) Antithrombin: Interference with antithrombin III activity has been described in patients with LA and thrombosis. Prekallikrein (Fletcher factor) may be inhibited in association with LA and consequence impairment of fibrin clearance is likely to promote clotting(17).

(v) Protein C system: In the normal state Protein C. system is key to inactivating factor Va and factor VIIIa. To do this requires thrombin and thrombomodulin. It is suggested that APA inhibits activation of protein C by thrombin-thrombomodulin and IgG preparation from LA positive plasmas have been shown to inhibit activated protein C (APC)(18).

(vi) Fibrinolysis: Increased level of plasminogen activator inhibitor activity (PAI) in patients with LA has been shown and increased PAI levels represent antihibiting factors of the fibrinolysis of clot with decreased fibrinolytic capacity and increased Von Willebrands factor levels as indicators of endothelial cell dysfunction in fibrinolytic activity patients with LA has also been demonstrated(19).

(vii) Platelets: LA is thought to bind to endothelial cells and platelets interrupting prostacylin production which in turn inhibits normal platelets adhesion and aggregation. Also platelet autoantibodies autoreactive have been demonstrated by some cases of LA. These were IgG antibodies to platelet protein antigens and patients who had them had history of thrombocytopenia thrombosis and LA. Further studies have shown there have been consistent elevations of urinary metabolites of thromboxane A_2, which show that there is *in vivo* activation of platelets(20). These could explain the hypercoagulation state in LA as a result of activation of the haemostatic system whose consequence is venous thrombosis and arterial occlusions leading to the protean manifestations. However there are cases of haemorrhagic diathesis caused by thrombocytopenia or factor II deficiency have been documented.

Clinical:

Some of the commonly vasoocclusive manifestations are as follows:

Vascular thrombosis and occlusions: While thrombosis of leg veins has been the most frequently reported form of deep vein thrombosis (DVT) and is often accompanied by pulmonary embolism, other vascular systems can be

affected. For instance axillary veins, superficial veins and involvements of the axillary artery giving rise to an aortic arch syndrome and mesenteric artery occlusions with resultant bowel infarction have all been demonstrated(21).

Skin: Cutaneous manifestations recorded are gangrene, superficial immigratory or just thrombophlebitis, ulcers and cutaneous necrosis and levido reticularis. Most patients who had these also had cerebral infarction(22).

Renal: Associations have been demonstrated with prominent renal vascular disease, renal thrombotic microangiopathy in the absence of proliferative glomerular lesions. Renal infarction occurred in a patient in the series of patients with chorea reported by Asherson et *al.*(23).

Central nervous system: Arterial occlusions of large cerebral arteries causing stroke and transient ischaemic attacks (TIAs) with amanurosis fugax are well known to occur in LA cases. Migraine often heralding the onset of a major cerebral catastrophe while epilepsy and chorea are not rare sequelae. Behavioural abnormalities like demetia and Gullian-Barre syndrome (GBS) have been reported in several patients. Other associated neurological syndromes include: cardiogenic brain embolism, late onset seizures, ischaemic stroke, cerebral vasculitis and dural sinus thrombosis(24).

Eye: Associated eye diseases are: retinal vein thrombosis, central retinal artery occlusion, also occlusive retinopathy usually associated with cotton wool spots infarcts of the nerve fibres layer of the retina(25).

Liver: Hughes reported thrombosis involving the inferior vena cava, hepatic veins associated with Budd-Chiarri Syndrome(26).

Heart: Myocardial infarction particularly in the young and thrombotic endocarditis mimicking rheumatic heart disease without history or other features of rheumatic fever are documented. Also association of LA and APA with severe valvular heart disease in patients with and without SLE are well documented(10).

Lungs: Lung diseases associated with LA include pulmonary thromboembolic hypertension in pulmonary embolism and just pulmonary hypertension(PHT) (26,27).

Haemorrhagic diathesis: Clinical and laboratory findings typical of idiopathic thrombocytopenic purpura (ITP) except for positive LA are well documented(12). Rarely in adults and children have LA been associated with a haemorrhagic diathesis caused by Factor II (FII) deficiency hypothrombinaemia. Usage of drugs such as quinine, quinidine and procainamide have been associated with LA particularly in the elderly. Similar associations have been registered in cases of ulcerative colitis and adrenal insufficiency(28).

Pregnancy related: In a prospective study of five hundred women with history of recurrent miscarriages for LA and a-CL antibodies, Rai *et al.* (29) found prevalence of 9.6% and for IgG and IgM and a-CL of 3.3% and 3.2% respectively. While in another review Haywood and Brown (30), observed approximately 10-15%, of all the patients undergoing recurrent pregnancy loss had LA whereas a-CL were found in 10-13%. Further obstetric associations include: foetal growth retardation early onset of severe pre-eclamptic toxaemic and chorea graviderum. In addition a severe post partum syndrome has been described consisting of fever, cardiac involvement and pleural effusion(11). Other described complications include HELLP syndrome accompanied by placental abruption, hepatic, dermal and adrenal infarction and decidual vasculopathy and often extensive placental infarction is found in many patients(27,30).

Childhood diseases: In the paediatric age group SLE, Juvenile Rheumatoid Arthritis (JRA) and overlap syndromes (OS), autoimmune haemolytic anaemia, pulmonary hypertension and neurologic alterations have been demonstrated with LA(12,31).

Laboratory tests: Laboratory features of LA are equally protean; however there have to be clinical indications and prior clotting test results to suggest how to approach testing for circulating anticoagulants(32).

Screening for anticoagulants primarily involve an activated partial thromboplastin time (APTT) in the patient's plasma alone and in an abnormal patients clotting test which does not correct adequately on mixing with normal plasma immediately or after incubation (usually 37°C for 2 hours). An inhibitor appearing to affect more than one clotting factors are probably LA since APTT is the first test of choice. Simple dilution of an APTT reagent or a phospholipid therein is a reliable method for enhancing sensitivity to LA(32). Other tests are; Kaolin clotting time (KCT) is basically APTT without phospholipid in the reagent, reclacification clotting time (RCT) is regarded as one of the most sensitive for detecting LA and dilute Russell's Viper Venom Time (dRVVT) test for LA overcomes some deficiencies that are observed in APTT like level of factor VIII levels. Specific immunoglobulin tests are assays for LA; IgG, IgM, IgA or mixture. Some immunological assays are designed to detect phospholipid antibodies using RIA or ELISA which may be necessary for antiphospholipid antibody IgG with IgG and IgG2 being the predominant subclasses of antiphospholipid antibody particularly in women with LA(33).

Other haematological findings are; thrombocytopaenia, which is a common occurrence but is not usually associated with haemorrhage, a haemolytic anaemia, antinuclear antibodies (ANA) and double strand DNA antibodies and (a-CL/ACA).

Associated anticardiolipin antibodies (a-CL/ACA): It is critical to evaluate patients' sample for both LA and ACA since the presence of ACA has the same clinical implications as that of LA due to the fact that in approximately 60% of circumstances both antibodies will be found(29,32,34). The author has found ACA in five of his cases (unpublished data).

In some SLE patients with a history of thrombocytopaenia and thrombosis particularly with arterial occlusions are platelet autoantibodies and an exceptionally strong reacting antibody directed against platelet protein antigens(35).

Venereal research laboratory test (VDRL) is often perfomed and is usually positive in absence infection by syphilis(4,35). Five out of six cases of LA identified in our setting have not been VDRL positive but negative Trepanoma Pallidum Haemagglutination test (TPIHA) (unpublished data).

Above all it is critical to evaluate patients on more than one occasion and a strong clinical evidence is vital for diagnosis.

Treatment: In general, therapeutic regimens should consider, the primary disease and associated factors. The choice of treatment regimes may then involve immunosuppresion using glucocorticosteroids, and high dose intravenous immunoglobulin (IVIG), and use of antiplatelet agents, anticoagulants drugs and plasmapheresis(36). Most alternatives are as follows: Aspirin alone in doses as low as 75 mg/day particularly in pregnancy have shown encouraging results from trials. However, the current focus of therapeutic modality combines roles of heparin and aspirin. Low molecular weight heparin (LMWH) and unfractionated heparin with the former, a preferred choice due to having higher antithrombotic ratio, meaning less bleeding for better antithrombotic effect, longer half-life and less heparin induced thrombocytopaenia in thrombosis associated with LA(36).

Success using cyclophosphamide and prednisone and a green yield filter inserted into the inferior vena cava of a LA associated with anti-neutrophil cytoplasmic antibody associated polyarteritis have been reported by Cohney *et al.*(37).

Oral anticoagulation with coumadin or warfarin in patients with a tendency to develop vascular occlusions and who have high titre of the antibodies is advised. In the use of oral anticoagulants it has been observed that standard intensity of oral anticoagulant therapy INR 2.0-3.0 did not suppress venous thrombosis recurrence, there is an emerging consensus that patients with APA should be treated more aggressively with oral anticoagulants (high intensity) with an INR of 3.0 to 3.5 (38).

Intravenous immunoglobulins (VIGs), specifically IgG therapy has been shown to result in transient suppression of LA but not anticardiolipin(36,37).

Other factors to be considered while treating, the LA cases are that people with IgM (more than 9 IgM body numbers) or low level of IgG (fewer than 20 IgG body numbers) antibodies comprise a distinct population from those with moderate to higher levels of anticardiolipin antibody. Such people are not at risk for thrombosis or disorders associated with antiphospholipid antibodies beyond the risk conferred by their medical histories. However, they warrant repeated testing with new or recurrent symptoms. People in the high positive group of LA of more than 19 IgG binding of anticardiolipin antibodies are more likely to develop at least one new medical complication than those in the low positive IgG. These patients need continuous treatment and follow-up. Furthermore patients who are persistently positive with LA or ACA and have a thrombotic history appear to be at increased risk for recurrence of approximately 50% over a five-year-period. Also if an individual initially experienced a venous thrombosis, the subsequent recurrence typically is venous(36-39).

It is important to realise that there is 'spill-over' of these antibodies to sections of the population not suffering from overt disease. Their prevalence in young patients with stroke, myocardial infaction and hitherto unexplained vascoulopathies should be explored and documented. Rather than attempt to reduce the antibody levels, it seems to be far easier to prevent their effect. This surely is important to the young patients.

In conclusion it is clear that LA has protean manifestations and can also imitate other diseases. For the diagnosis strong index of suspicion should be based on the history of thrombotic events, pulmonary hypertension, unexplained thrombocytopenic or repeated foetal losses. Treatment should be aimed at the underlying factors, controlling the symptoms and the prevailing LA syndrome.

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