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Antiphospholipid antibody syndrome: two case reports and review of literature

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Summary
Antiphospholipid antibody syndrome (APAs) is an acquired multisystemic disorder characterised by hyper coagulation. It manifest clinically with arterial and venous thrombosis. It is not a rare phenomenon, but there are paucity of reports of this disorder in our environment. We present two cases of APAs with the hope that it will stimulate the awareness of clinicians in the recognition of this disorder in our environment.

Résumé
Le syndromr des anticorps aux phosopholipides (APAs) est un desordre multi systemique acquis characterise par e'hypercoagulation. I lse manijeste cliniquement par une thrombose gles artivies et des veines. Le n'est pas un phenomene rare, mais il ya des cas rares de reports de le gense de desordre dans votre enironment. Nous presentons L las dapas avell l'espir que cela stimulera la prise de conscience des cliniciens dans la reconnaissance de le desordre donurs rotre environment.

Introduction

The Antiphospholipid Antibody syndrome (APAs) is an acquired multisystemic disorder characterised by hyper coagulation[1]. The clinical manifestations include arterial and venous thrombosis, recurrent fetal loss and thrombocytopenia. Serological markers for this disorder are the antiphospholipid antibodies the anticardiolipin antibodies and the lupus anticoagulant[2].

There is a paucity of reports of this disorder in this environment. We report 2 cases of antiphospholipid antibody syndrome in the University College hospital Ibadan.

Case 1

A 30 year old lady was referred to the Department of Medicine of the University College Hospital Ibadan (UCH) with a 14week history of double vision, headache and weakness on the left and right side of the body. She had enjoyed relatively good health until she developed diplopia which was worse on looking to the left. About 6 days later she noticed she had weakness on the left upper and lower limbs and drooling of saliva from the angle of the mouth. Two days later she then had weakness on the right side of the body as well and could no longer walk. There was accompanying headache but there were no seizures nor loss of consciousness. There was no previous history suggestive of transient ischeamic attacks. She had not noticed any rash on her face and there was no history of a febrile illness, arthralgia, or arthritis preceding the illness. There was no history of hypertension or diabetes.

Her obstetric history revealed a normal delivery of a live baby 4 years ago after which she had 4 spontaneous first trimester abortions in the last two years. She had not had any gynaecological surgeries, e.g., dilatation and curettage in the past.

Examination revealed a young woman who was afebrile, anicteric and not pale. There was no significant peripheral lymphadenopathy. She had livedoreticularis on the palms and soles. She had superficial ulcers on the buccal mucosa. Examination of the central nervous system revealed spastic quadriparesis, bilateral upper motor neuron facial nerve palsy. The left side was more affected than the right. She had a sixth nerve palsy on the left. She also had global aphasia. The cardiovascular, respiratory and abdominal examination were normal.

A working diagnosis of antiphospholipid antibody syndrome was made. The following investigations were ordered which gave the following results. A computerized axial tomography (CAT scan) showed a right parietal infarct. However this could not account for the quadreparesis, she may have had some small lacunar infarction which where not picked up by the CT scan. The full blood count showed a pcv 32% and a total wbc of 8,600, with normal differentials. The of platelet count was 213,000 and the ESR 48%. The clotting profile Venereal Disease Research Laboratory (VDRL) was negative. LE cells were absentScreening for the lupus anticoagulant using the APTT method was positive. There were no facilities for detecting anticardiolipin antibodies. The patient was commenced on Warfarin and Prednisolone. Livedo reticularis and mouth ulcers cleared. She was discharged to the out patient clinic to continue physiotherapy and to have monitoring of her clotting profile.

Case 2

A 36 year old lady who had been managed to secondary infertility was seen in the gynecology clinic with a history of lower abdominal pain. She was then 14 weeks pregnant. She was Para 2 + 4 with 2 alive. She was frightened because of the lower abdominal pain which she said had preceded the last 4 pregnancies. The first 3 of the abortions were spontaneous and occurred in the late first trimester the last one was a case of intrauterine death in the second trimester.

There had been no febrile illness preceding the abortions. She had not used contraceptive pills in the past and she did not have any previous gynaecological surgeries s e.g. dilatation and curettage. There was no history of any underlying diseases. The patient was otherwise in relative good health.

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Examination revealed a healthy looking lady. She had hyperpigmented patches on both malar area suggestive of exogenous onchronosis from use of skin bleaching creams containing hydroquinone. Examination of all the systems were essentially normal. Pelvic ultrasound showed a life fetus 14 weeks size. She was admitted into the wards. She was placed on bed rest, ventolin (salbutamol) and diazepam. While on the wards she began to bleed per vagina which increased gradually. A repeat ultrasound showed an 18 week fetus, cephalic presentation. There was no evidence of fetal heart activity, or fetal movement. The fetal outline was poor due to scanty liquor. The umbilicus was seen floating below the presenting part. The internal Os was closed. Patient had evacuation of the fetus.

The following investigations were ordered. The pcv was 34%, total WBC 5,000, platelet count 208,000. The PT ratio 1:1, PTTK test 56 control 37. The lupus anticoagulant was present using the APTT. Histology of the placentae revealed areas of heamorrhage and infarcts. The cord appeared normal. There was maceration of the fetus but there was no gross abnormality. A diagnosis of primary antiphospholipid antibody was made.

Discussion

APAs is an acquired multisystemic disorder characterized by hyper coagulation [1]. Other synonyms for APAs include anticardiolipin or lupus anticoagulant thrombosis syndrome2 and the Hughes syndrome1 (recognising one of the physicians who initially described the syndrome).

The APAs is classified into two; 3 The primary APAs in which there is no underlying associated disorder and the secondary type in which there is an associated underlying disorder, e.g., systemic lupus erythematosus (SLE), rheumatoid arthritis, malignancies, infections, and use of certain drugs (Table 1).

Table 1: Causes of secondary antiphospholipid antibody syndrome.

Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Systemic sclerosis
Dermatomyositis
Diabetes mellitus
Myasthenia gravis
Infections
Bacterial (syphilis, leprosy,
Tuberculosis, Lyme diseases)
Viral (HIV, Hepatitis, infectious
Mononucleosis
Malignancy
Lymphoproliferative disorders
Leukaemias paraproteinaemias
Solid tumours
Hematological diseases
Polycythaemia rubra vera
Myelofibrosis
Vasculitic
Behcet's disease
Drug associated
Hydrallazineprocainamide

There is a higher incidence of the primary type of APAs [2]. The auto antibodies which are responsible for the disorder are the antiphospholipid antibodies; anticardiolipin and the lupus anticoagulant. From laboratory findings, the APAs can be separated into 2 closely related but distinct clinical syndrome subsets, the anticardiolipin APAs and the lupus anticoagulant APAs. The anticardiolipin antibodies are more prevalent than the lupus anticoagulant in a ratio of 5:14. Although a high correlation exists between the anticardiolipin antibodies and the lupus anticoagulant occasionally one occurs without the other being present especially in the primary APAs[3]. We feel this may contribute to low reporting of the syndrome in this environment as screening facilities for the lupus anticoagulant is more readily available than for the anticardiolipin antibodies.

The pathogenesis of the disorder is not fully understood but various hypothesis have been put forward to explain the events that occur. The antiphospholipid antibodies were initially thought to be directed against anionic phospholipid1, but studies now show that the auto antibodies show specificity for different phospholipid binding plasma protein resulting in procoagulant activity in vivo and thrombosis[5,6]. Hypothesis for the possible effects of the reaction of the antibodies and phospholipids are outlined below. These include endothelial membrane damage[9] interfering with prostacyclin production from the endothelial lining [8], leading to platelet activation [7], interference with antithrombin III activity and impairment of fibrinolytic mechanisms [10]. Interference with protein C and S anticoagulant pathways[9] . It also leads to inhibition of phospholipid placental anticoagulant protein 1 thereby leading to obstetric complications[12]. It is believed that all these factors contribute to the formation of non-inflammatory thrombosis in the arteries and veins. Phospholipids are important in some critical steps in the intrinsic and extrinsic coagulation pathways. Antiphospholipid antibodies impair some of this steps. This explains why test like the activated partial thromboplastin test are used to detect the lupus anticoagulant.

Auto antibodies from the autoimmune disorder require the presence of a plasma co-factor B2-glycoprotein (B2-GPI) or apolipoprotein H[5,13]for binding to phospholipids. The B2 GPI has been found to have anticoagulant properties in *vitro* [14]. The anticardiolipin and B2-GPI phospholipid complex however has been found to have procoagulant effects leading to thrombosis[15]. Antiphospholipid antibodies produced in infection do not require the B2-GPI for binding. This may explain the absence of thrombosis in patients with antiphospholipid antibodies due to infections.

The clinical features of the APAs are as a result of vascular occlusion and thrombosis in the arteries and veins in various organs (Table 2).

Table 2: Clinical manifestation of thrombosis in APAs

Venous occlusion
Deep venous thrombosis
Renal vein thrombosis
Retinal vein thrombosis
Budd- Chiari syndrome
Pulmonary embolism
Arterial occlusion
Myocardial infarction
Cardiac valvular abnormalities
Cerebrovascular accident (ischaemia)
Transient ischeamic attacks
Multi infarct dementia
Limb ischaemia, gangrene
Mesenteric infarction
Hepatic infarction

It is not usual to differentiate the anticardiolipin and the lupus anticoagulant APAs clinically although the lupus anticoagulant tends to produce more of venous thrombosis.[3]Cutaneous features occur commonly in these patients and may be a presenting sign of the illness. A previous study showed that 41% of patients with APAs presented with cutaneous manifestation and later developed other thrombotic complications during the course of their illness.[16] Livedo reticularis is the most common cutaneous manifestation [2,17,18]. It appears as dusky violaceous discoloration of the skin with a network appearance of blood vessels due to the sluggish movement of blood in the superficial drainage system. It is usually found on the palms, soles, and extremities. In dark coloured skin it would be difficult to detect the colour change on the glaborous skin. Other cutaneous findings include splinter hemorrhage, leg ulcers (usually pre-tibia), purpura, echymoses, cutaneous gangrene and necrosis of the skin. Less common disorders include anetoderma, discoid lupus erythematosus, progressive systemic sclerosis and cutaneous T cell lymphoma.

The neurological manifestations are usually due to arterial thrombosis. Transient ischaemic attacks and cerebral ischaemia are the commonest manifestations [19]. Recurrent events especially multiple strokes are common. A study carried out on patients with ischaemic cerebrovascular accidents (CVA) showed that 46% of patients below the age of 50 years had antiphospholipid antibodies [20]. This would imply that all patients with ischeamic CVA without obvious risk factors should be screened for antiphospholipid antibodies. Other neurological manifestations include seizures [21], migraine [22], myasthenia gravis [23] and pseudotumour cerebri [23].

Obstetric complications are not uncommon in female patients with antiphospholipid antibody syndrome. Both of our patients had recurrent abortions. Proposed mechanisms for this complication include decidual vasculopathy leading to impaired prostacyclin production [24], thrombosis and infarction [25] and impairment of embryonic implantation [21]. There is a high risk of fetal wastage due to spontaneous abortion at the end of the first trimester and increased incidence of intrauterine death during the second and third trimester. Abnormal pregnancies usually begin with apparent normality, with or without thrombocytopaenia, slow fetal growth and decrease in amniotic fluid. The placenta are small with non-inflammatory vasculopathy [27]. Prior fetal loss in this patients is a significant independent predictor of fetal loss [2]. High maternal antibody titer are associated with a syndrome of high spiking fever, pleuritic chest pain, dyspnoea, pulmonary embolism, and cardiomyopathy occurring 2-10 days post partum[2].

Thrombosis

Recurrent venous and arterial thrombosis is a major feature. Deep venous thrombosis occurs commonly and may lead to pulmonary embolism [28]. Venous thrombosis affecting the retinal, renal and hepatic veins with Budd- Chiari syndrome. Arterial thrombosis involving the carotid, hepatic and splenic, mesenteric and retinal arteries have been documented. Retinal artery thrombosis associated with APAs can develop at any location within the renal vessels leading to various abnormalities; proteinuria, systemic hypertension, cortical necrosis thrombotic microangiopathy and renal failure.

Cardiovascular disorders including coronary thrombosis leading to myocardial infarction has been documented. Libman- sacks endocarditis is seen in a few patients with SLE and APAS

Thrombocytopenia

This occurs commonly in APAs. The exact mechanism is not known, but enhanced platelet destruction and probably removal of antibody coated platelet from The circulation may be contributory.

Laboratory investigation

At present the antiphospholipid antibodies are detected through different tests. Both set of antibodies should be sought for in all patients being investigated for the APAS. Both antibodies may be present in a patient. In some patients you may have either the lupus anticoagulant or the anticardiolipin antibodies being present. Patients who have both seem to have similar prognosis to those who have either antibody alone. The anticardiolipin antibody was initially detected by solid-phase radio immunoassay, but the enzyme-linked immunosorbent assay (ELISA) is now available for identifying the antibodies. It detects antibodies which are mainly of the immunoglobulin (Ig) G, M and A isotypes. It is generally agreed that high titres of Ig G anticardiolipin antibodies are found to be more clinically relevant than Ig M type of antibodies in predicting the occurrence of thrombosis, thrombocytopeania and recurrent abortion [29]. The IgM antibodies occur commonly in infections. The IgA isotypes are important in patients with SLE.

Anticardiolipin antibodies present in some infections and some autoimmune disease are now known to be responsible for the biological false positive reactions obtained with the Venereal Disease Research Laboratory test(VDRL) [30]. Not all patients with antiphospholipid antibodies give a false positive VDRL reaction. It is therefore not the ideal screening test. The ELISA kits for detecting anticardiolipin antibodies are not easily available presently in this environment. We had to use the VDRL test in out patients understanding its limitations.

The lupus anticoagulant is actually a misnomer because the antibodies exhibit pro-coagulant activity in vivo and most patients do not have systemic lupus erythematosus. The antibodies are of the IgG and IgM isotypes. They interfere with in vitro phospholipid dependent coagulation test. Several test such as the APTT, Kaolin clotting time (KCT), and the dilute Russell viper venom time (dRVVT) are used for screening for the LA. Other test used include Textarin time (TTI), platelet neutralization procedure (PNP) and dilute tissue thromboplastin inhibition test are less frequently used. The APTT has been used for screening for the presence of the lupus anticoagulant although it is not sensitive when the titres of the antibodies are low [2]. A report from this environment has showed that the adoption of an APTT correction ratio will enhance its reliability [31]. Confirmation test such as TTI, dilute RVVP can then be carried out. Current evidence suggest that the lupus anticoagulant is a better predictor of thrombotic complications than the antiphospholipid antibody measured by ELISA but that a high titer of antiphospholipid antibody denoted by ELISA is more sensitive for identifying pregnancies at risk for fetal death [32].

Other relevant test in patients with APAs include a blood count and film. The presence of thrombocytopenia is suggestive of the syndrome. The absence of fragmented cells, fibrin split products and haemolysis helps to distinguish this syndrome from thrombotic thrombocytopeanic purpura, haemolytic ureamic syndrome and disseminated intravascular coagulation.

Studies elsewhere have shown that about 2% of the normal population have antiphospholipid antibodies with some of them having high titers and without features of thrombosis [33].

In making a diagnosis of APAs, patients must have arterial or venous thrombosis, a history of recurrent fetal loss or thrombocytopenia with the presence of the antiphospholipid antibodies (lupus anticoagulant and, or anticardiolipin antibodies) (table 3). In the management of patients with fetal loss, a previous report has shown that screening all women with single fetal loss is generally uninformative. They found that fewer than 2% of women who gave a history of single fetal loss had APAs while approximately 10% of women with two or more losses

Table 3: The diagnosis of antiphospholipid antibody syndrome

Major Criteria
Arterial thrombosis
Venous thrombosis
Recurrent fetal loss
Thrombocytopenia
supportive clinical finding
Livedo reticularis
Diagnosis
One major criterion in conjunction with lupus anticoagulant of high titer anticardiolipin antibody.

had APAs. They felt that screening patients with a history of recurrent, i.e., 2 or more incidence of fetal loss would excludemany of those with non recurring miscellaneous causes of pregnancy loss.

We feel that patients with a history of single fetal loss in the absence of known factors should be screened for this syndrome, since a prior fetal loss in these patients is a significant independent predictor of fetal loss2. There is paucity of reports of APAs in our obstetric cases in this environment, we believe more studies should be carried out to address this disorder. Prophylaxis and treatment of thrombosis relies mainly on anticoagulant and antiplatelet therapy.

There have been no studies to indicate that prophy lactic treatment is useful in patients with APAs in the absence of thrombosis, but patients with high titre of antibodies may be advised to avoid associated risk factors such as smoking, use of oral contraceptive agents and adequate supervision of hypertension when present. Such patients require propylactic heparin therapy when they require to stay in bed for long periods of time.

In patients with thrombotic episodes anticoagulation with Warfarin is the treatment of choice. Recurrence of thrombosis is known to occur after stopping anticoagulation and so long term therapy is advocated, probably for life. The dose of Warfarin is adjusted so as to keep the international normalized ratio (INR) between 3 and 4 [34]. There is a high incidence of Warfarin resistance be these patients and high doses may be needed [35]. If thrombosis progresses despite adequate anticoagulation aspirin may added. In patients who present mainly with superficial venous thrombosis aspirin may be adequate.

A lot of work has been carried out on patients with recurrent fetal loss as a result of the APAs. The current management advocates that in patients with more than 2 fetal losses from APAs they should receive aspirin 75 mg for the first 12 weeks, heparin till 32nd week of pregnancy and return to aspirin for the remaining weeks of pregnancy[36]. In patients with one fetal loss and high titer of antiphospholipid antibodies aspirin alone may be sufficient. Immunosuppressive therapy is now restricted to secondary APAs for the treatment of the underlying disorders and in patients who have catastrophic vascular occlusion syndrome. In making a diagnosis of APAs a high suspicion is needed. Patients presenting with hypercoagulable states should be screened for APAS. Further studies are needed to find out its incidence and the morbidity it imposes in this environment.

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