Antiphospholipid Syndrome, Familial

Alternative Names
APS
Lupus Anticoagulant, Familial
Hughe's Syndrome

Record Category
Disease phenotype

WHO-ICD
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism > Coagulation defects, purpura and other haemorrhagic conditions

Incidence per 100,000 Live Births
11-50

OMIM Number
107320

Mode of Inheritance
Autosomal dominant

Gene Map Locus
N/A

Description
Antiphospholipid syndrome (APS) is a clinical disorder characterized by recurrent arterial and venous thrombotic events, fetal losses, thrombocytopenia, neurological symptoms, livedo reticularis, and hemolytic anemia. Affected individuals show persistently elevated levels of antibodies directed against cellular phospholipid components (aPL). APS can occur in patients with or without evidence of any definable associated disease, in which case it is referred to as primary APS. It may also occur in association with another rheumatic or autoimmune disorder, such as Systemic Lupus Erythematosus (SLE, hence Secondary APS).

Incidence of antiphospholipd syndrome remains unknown. However the reported prevalence of antiphospholipid antibodies in the general population is low (1-4.5%) and increases with age. The antiphospholipid antibodies have been detected in approximately one-third of the patients with SLE. High anticardiolipin antibodies titers, lupus anticoagulant (LAC) and especially anti-beta2GPI antibodies are important predictors of APS clinical manifestations in SLE patients. A rare form of this disease is the catastrophic APS, in which there is rapid organ dysfunction and failure. The management of thrombosis includes long-term, high-intensity warfarin therapy. For pregnancy morbidity, the recommended therapy is low-dose aspirin (80 mg/day) plus subcutaneous unfractionated heparin or low-molecular-weight heparin.

Molecular Genetics
The aPL antibodies belong to the large family of antibodies that react with negatively charged phospholipids, such as cardiolipin, phosphatidylglycerol, phosphatidylinositol, as well as beta-2 glycoprotien, prothrombin, annexin V, Protien S, and high molecular weight kininogen. The predisposition to clotting characterized in this disease is predominantly due to these antibodies interfering with the antithrombotic role of phospholipids such as cardiolipin, causing platelet aggregation and subsequent vascular occlusion. APS, therefore, is associated with thrombotic, rather than hemorrhagic complications. Familial occurrence of elevated levels of aPL antibodies, as well as an association with HLAs DR4, DR7, DQ7, and DR53 have been reported.

Epidemiology in the Arab World
Bahrain

Rajab et al. (2002) reported three cases of antiphospholipid (Hughes) syndrome during pregnancy in women at Manama. Subjects with antiphospholipid antibodies experienced several clinical problems including infertility, recurrent miscarriage, increased perinatal mortality, episodes of thrombosis during pregnancy and puerperium. The first case represented a 35 year old Bahraini who suffered from recurrent abortions, sickle cell disease, and antiphospholipid syndrome throughout pregnancy. She was treated with heparin prophylaxis and delivered at 38 weeks gestation through Cesarean section, but she passed away postnatally due to substantial pulmonary embolism. Case 2 represented a 28 year old female who was admitted into the hospital at 8 weeks gestation suffering from cerebro-vascular accident. The subject was treated and recovered well, but her pregnancy was terminated. Case 3 represented a 31 year old Bahraini with a history of infertility. She was treated with heparin prophylaxis and delivered a healthy live baby boy. Rajab et al. (2002) suggested screening all pregnant women having bad obstetric history or recurrent miscarriages.

Ebrahim et al. (2005) undertook a study on 22 Bahraini patients with APS over a period of 16 years. Among these patients, the frequency of primary APS was 45.8%, while secondary was 54.5%. Female:male ratio was 10:1. The percentage of pregnancies was 71.4%, and 57.1% of these ended in miscarriages (80% in primary and 50% in secondary APS). Anticardiolipin IgG and IgM were assayed by ELISA. Ebrahim et al. (2005) found that the aCL IgG was higher in primary APS (80%) as compared to secondary APS (66.7%). However, aCL IgM was higher in secondary (75%) compared to primary APS (60%). Earlier reports have suggested that patients with IgG aCL antibodies are at higher risk than those with IgM or IgA antibodies. Antinuclear antibodies were present in all of the secondary APS, and in 20% of the primary APS patients. Treatment given to the patients was either in the form of aspirin (33.3%), steroid (76.2%), heparin (28.6%) or warfarin (28.6%). Ebrahim et al. (2005) concluded that APS is not a common problem among hospitalized patients in Bahrain.

Al Jishi et al. (2005) described, for the first time, a 41-year-old married woman with a combination of Takayasu arteritis (TA) and primary antiphospholipid antibodies (aPL) syndrome who underwent carotid stenting. In the first observation, she had a normal ECG. After eight years, early vasculitis was detected on biopsy from erythematous skin lesion. Also, her upper limb pulses were weak and a weak flow through the right radial was noticed by ultrasound. One year later, she was admitted to neurology ward with history of dysarthria of acute onset. She was suffering from bronchial asthma for 15 years. On examination, she was obese, and her speech was slurred. She had upper motor neuron left facial palsy, and left carotid bruit. Human lymphocyte antigen (HLA) analysis was obtained showing that the patient had HLA-A2 and A9 which were susceptibility alleles for TA in Arabs. She underwent CCA stenting, however she did not receive steroids that would prevent restenosis because she could not tolerate it. She developed acute episode of aphasia four months after the stenting.

Al-Naqdy and Al-Shukaily (2005) tested patients with SLE (30 patients), recurrent abortions (44), and thrombosis/thrombocytopenia (36) for the presence of anticardiolipin (ACA) and anti beta2-glycoprotein antibodies. All groups of patients showed a significantly higher frequency of the antibodies, ACA (SLE-23%, recurrent abortions-27%, thrombosis-36%) and anti beta2 GP (SLE-16.6%, recurrent abortions-18%, thrombosis-22%), when compared to 30 age and gender matched healthy controls (ACA-6%, anti beta2 GP-3%). Both antibodies were detected in 10% of the SLE patients, 13.6% of the patients with recurrent abortions, and 1.4% of patients with thrombosis. Incidentally, all patients with SLE who showed the presence of both antibodies also showed clinical characteristics of thrombosis/thrombocytopenia. Al-Naqdy and Al-Shukaily (2005) suggested that both antibodies be used together in the diagnosis of APS, in order to circumvent the lack of specificity of ACA.

Egypt

[See: Kuwait > Malaviya et al., 1996].

Kuwait

Malaviya et al. (1996) carried out a prospective study to report Hughes (Antiphospholipid) syndrome cases for the first time in the Middle East at two major hospitals in Kuwait (Mubarak Al-Kabeer and Amiri Hospitals). The study included 32 patients with Hughes syndrome with 12 subjects experiencing the primary type (aged 20 to 61 years) and 20 subjects experiencing the secondary type (aged 18 to 50 years). The female to male ratio was found to be 1.4:1 and 9:1 for subjects with primary form and secondary form, respectively. Out of the 12 subjects with primary form, six were Kuwaitis, five Egyptians and one patient was a Middle-Eastern Arab, while out of the 20 subjects with secondary form 12 were Kuwaitis, five Egyptians and two Middle-Eastern Arabs. Thrombosis (both arterial and venous) was found to be the most common clinical manifestation followed by fetal wastage. A female patient suffering from primary Hughes syndrome passed away due to massive inferior myocardial infarction while other four patients were treated in the intensive care for pulmonary embolism and three of them needed emergency vascular surgery. An estimated prevalence of Hughes syndrome was found to be 2.66/1000 admissions in medical wards.

Abdulmalik and Al-Ateeqi (2003) reported an Arab infant who suffered from a stroke as a symptom of antiphospholipid syndrome (APS) at Al-Amiri Hospital. The patient was born in a full term breech delivery with a birth weight of 3.6kg. He was the third child born for healthy non-consanguineous parents. The infants' mother experienced two abortions prior to his birth and one abortion after the patient was born. It was found that APS patients are classified as having at least one clinical and one serological characteristic throughout their illness. The clinical characteristics include venous thrombosis, arterial thrombosis, recurrent fetal loss and thrombocytopenia; whereas the serological characteristics include either positive lupus anticoagulant (LAC) test or positive IgG and/or IgM anticardiolipin antibodies (aCL) at moderate to high level. The patient fulfilled the APS criteria. He is thought to be the first case of primary APS in an infant in the Gulf Region.

Oman

Venugopalan et al. (2001) reported the accidental finding of lupus anticoagulant in two children with heart disease when they were preoperatively investigated. The first case was a six month old girl who was admitted for surgery for patent ductus arteriosus. She was on digoxin and frusemide for three months and had an attack of upper respiratory tract infection one week prior to admission. Clinically, she had signs of a large patent ductus arteriosus and hepatomegaly (due to heart failure), but no splenomegaly or lymphadenopathy. Investigations revealed normal hemoglobin and blood counts, normal ESR (6mm/hr), normal prothrombin time (12 seconds) but prolonged activated partial thromboplastin time (APTT) of 61 seconds which could not be corrected with normal plasma. Assays for plasma fibrinogen, coagulation factors VIII, IX, XI, and XII, protein C, protein S and antithrombin were normal, but she was positive for lupus anticoagulant which was confirmed by hexagonal phospholipids neutralization procedure. Her blood cultures, throat swabs, antibody titers for adenovirus and respiratory syncytial virus were negative and so were antinuclear antibodies, anti-double stranded DNA and anticardiolipin antibodies. The second case was an eleven years old girl who was admitted for surgical management of her severely stenotic rheumatic mitral valve. She had no recent history of infection and had no hepatosplenomegaly, lymphadenopathy or skin rash. Investigations revealed normal blood counts but a raised ESR of 25mm/hr was detected along with prolonged APTT of 51 seconds, which was uncorrectable with normal plasma. She was found to have positive lupus anticoagulant, but other investigations (like in the first patient) were normal. Cardiac surgery was done to both patients without any complications and both showed persistent positive lupus anticoagulant after two and six months of follow up. Venugopalan et al. (2001) classified both patients as having the childhood form of lupus anticoagulant. Two years later, Al-Kiyumi and Venugopalan (2003) reported on a rare case of acute heart failure due to dilated cardiomyopathy, secondary to antiphospholipid syndrome. The patient was an 11-year-old boy, who presented with dilated cardiomyopathy, and left ventricular thrombi on ECG. Anticardiolipin antibodies were found to be elevated, and the patient later, went on to show thrombotic episodes of multiple organs. He later succumbed to multiple organ failure.

Qatar

Saad et al. (2000) performed a review of cases of Intra-Uterine Fetal Death (IUFD) in Qatar. Of the 10,188 births that took place in the year 1997, a total of 83 were still-born. Two of these still births were attributed to antiphospholipid syndrome, giving the condition an incidence of 0.2 per 1000 births and 2.4 per 100 still births.

In a study by El-Menyar et al. (2006) analyzing data pertaining to all patients less than 50-years of age, who were hospitalized between 1996 and 2003 with cardiomyopathy in Qatar, a rare association was noticed in one patient with dilated cardiomyopathy and APS. The patient was a 38-year old male with a reduced ejection fraction (21%), but normal coronaries. According to El-Menyar et al. (2006), this was the first report of comorbidity with these two conditions.

Saudi Arabia

Owaidah et al. (2003) conducted a single center review of clinicopathological characterization in patients with lupus anticoagulant (LAC) antibodies.

Screening tests included activated partial thromboplastin time (aPTT), diluted Russel's viper venom time, and Kaolin clotting time. Anticardiolipin IgG and IgM were assayed by ELISA. Indirect fluorescence procedure for antinuclear antibodies and noncompetitive EIA for ds-DNA antibodies were also used. The most frequent clinical findings were arterial and venous thrombosis, and obstetric complications. Owaidah et al. (2003) found a sizable number of patients with incidental APS. Also, in a majority of the cases, the activated partial thromboplastin time (aPTT) was elevated and was not corrected by mixing with normal plasma. The prothrombin time (PT), however, was normal in most of the patients.

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