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Anti-phospholipid syndrome: clinical spectrum and therapeutical/prophylactic strategies in the pediatric population

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Abstract. – Anti-phospholipid syndrome (APS) is a potentially life-threatening autoimmune condition characterized by the presence of anti-phospholipid antibodies (aPL) giving rise to increased hypercoagulability, which induces venous or arterial thrombotic events at whatever age and recurrent fetal loss in the fertile age. Antigens that are targeted by aPL include cardiolipin and beta$_2$-glycoprotein I. Primary APS is defined in the absence of an underlying disease, while secondary APS is observed in the context of another established pathological condition. APS has a wide variety of clinical signs and serological characteristics. This paper describes the current approaches towards diagnosis, therapeutic modalities and secondary prevention applied to children.

Key Words:

Anti-phospholipid syndrome, Children.

Introduction

Anti-phospholipid syndrome (APS) is a disorder described for the first time in 1980 characterized by the presence of anti-phospholipid antibodies (aPL) in the serum and by a clinical picture which can display intravascular thrombosis (in subjects of whatever age) or pathologic exits of pregnancy (in fertile women). APS represents the most frequent cause of acquired thrombophilia also in the pediatric age[1]. An alteration of the homeostatic regulation of blood coagulation occurs. However, the mechanisms of thrombosis are not yet defined. A pivotal role in the pathogenesis of APS is carried out by aPL, which are specific markers for APS: they include a heterogeneous group of antibodies and recognize various negatively-charged anionic phospholipids as cardiolipin, phosphatidylserine, phoshatidylethanolamine and phosphatidylinositol, but mainly phospholipid-binding proteins and phospholipid-protein complexes. Their most relevant effect is the interference with phospholipid-dependent coagulation assays and the subsequent prolongation of clotting times. Various theories have tried to explain the thrombophilic capacity of aPL. A first theory hypothyzes that various coagulation proteins bind membrane phospholipids of endothelial cells presenting a defective apoptosis with subsequent creation of aPL, targeted towards the new epitope phospholipid-protein complex, activating directly the vascular endothelium. Other proposed mechanisms for the hypercoagulable effect of aPL include activation of platelets to enhance endothelial adherence and predisposition to thrombosis, production of antibodies against coagulation factors, including prothrombin, protein C and S, naturally provided with the faculty of inhibiting clotting factors, and reaction of aPL to oxidized low-density lipoproteins, with subsequent damage to the endothelial cells which predisposes these individuals to atherosclerosis and myocardial infarction[2].

General Features of the Anti-phospholipid Syndrome

The simultaneous presence of aPL in the serum and thrombotic events defines the APS: aPL serologic positivity consents to assess a risk of 0.5-30% for new thrombotic episodes[3]. Thrombosis can involve whatever vascular district, both venous and arterial: in the child deep veins of limbs are the most involved vessels with

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the subsequent risk of pulmonary embolism, followed by cerebral and coronary arteries[4]. During the fertile age APS is basically characterized by pregnancy complications which follow intra-fetal or intra-placental thrombotic events and infarctions, which give rise to recurrent first-trimester miscarriage, second- or third-trimester fetal death and premature childbirth[5]. Three classes of aPL are historically associated with APS: lupus-like anticoagulant (LAC), anti-cardiolipin antibodies (ACL) and anti-β_2-glicoprotein I antibodies (Aβ_2GpI)[6]. In particular, the antigen specificity of LAC is still poorly characterized and oxidized phospholipids or plasma coagulation proteins are believed to be its main target. LAC, interfering with clotting factors X and V, as well as platelets and prothrombin, can be detected indirectly measuring the activated partial thromboplastin time (or aPTT), kaolin clotting time and diluted Russell's viper venom test which appear prolonged. ACL were discovered in 1983, react primarily to membrane phospholipids, such as cardiolipin and phosphatidylserine, are quantified with radio-immunologic assay and mostly IgG isotype correlates with the thrombotic events. Aβ_2GpI, directed towards β_2-glicoprotein 1, also known as apolipoprotein H, a natural anticoagulant substance capable of binding negative-charged phospholipids, were discovered in 1990 and are believed to be the main effectors of APS[7,8]. Although aPL are clinically linked to APS, whether they are the triggers of this pathology or a mere epiphenomenon of the disease is unclear. It is known that aPL occur in up to 5% of healthy individuals, both children and adults. aPL prevalence is higher in healthy children (5-20%) in comparison with the one observed in healthy adults (1-5%), though the clinical relevance of this difference is still debated[9].

Variants of Anti-phospholipid Syndrome

APS can occur in patients without any evidence of an associated disease (*primary APS*) or in association with systemic lupus erythematosus and other established rheumatologic/autoimmune disorders or diseases which are not mediated by the immune system, (*secondary APS*)[10]. The most recent study coordinated by Cervera et al. in over 1000 patients has revealed that 37% of APS is associated with systemic lupus erythematosus[11]. Sometimes APS arises in subjects with neoplasms, infectious diseases, after vaccinations (with recombinant hepatitis B vaccine and influenza virus vaccine) or in consequence of specific drugs, which might ultimately provide a clue to the etiology of APS, as shown in the Table I[12]. Recent literature suggests that the occurrence rate of APS in adult patients with systemic lupus erythematosus is 34-42%, but no epidemiologic data are available for pediatric patients. The prevalence of serologic aPL positivity is 30% in children with juvenile idiopathic arthritis, independently from the evidence of thrombotic complications[13]. It is mandatory to underline the possibility of a "catastrophic" variant of APS, also known as *Asherson's syndrome*, caused by the large production of microthrombi in various vascular districts and characterized by accelerated systemic involvement leading to multi-organic failure with massive thromboembolism and infarctions in central nervous system, kidneys, lungs and liver. Among the precipitating factors of a "*catastrophic*" APS we have to list infections, surgical procedures, anticoagulant treatment interruption, oral contraceptives and neoplasms[14,15].

Anti-phospholipid Syndrome in the Pediatric Age

The major part of clinical manifestations described in adults with APS have been reported in children too. From the revision of 50 pediatric patients with history of APS it has been observed that the female sex is more frequently involved, that the onset age is extremely variable (from the first infancy until the late adolescence) and that only a small percentage of patients displays a positive familiarity for clinical events which seem aPL-related[12]. The presentation clinical pictures of APS include venous or arterial vascular thrombosis, listed in the Table II[16]. Superficial or deep veins of the inferior limbs are the sites preferably affected by thrombotic events in 29-55% cases. Sometimes pulmonary embolism can be observed, but it seldom gives rise to pulmonary hypertension. Other sites of venous thrombosis include inferior and superior vena cava, renal, mesenteric, hepatic and retinic veins. Cerebral arteries are the sites where arterial thrombosis are most frequently diagnosed, resulting in transient ischemic attacks (TIA) or true

Table I. Diseases associated with anti-phospholipid antibody positivity.

Systemic autoimmune diseases	Systemic lupus erythematosus
	Rheumatoid arthritis and juvenile idiopathic arthritis
	Systemic scleroderma
	Sjögren syndrome
	Dermatomyositis
	Vasculitic syndromes
	Polyarteritis nodosa
	Cutaneous leukocytoclastic vasculitis
	Behçet's disease
Infections	Viral
	Acquired immunodeficiency syndrome (AIDS)
	Infectious mononucleosis
	Parvovirus B19-caused diseases
	Hepatitis C
	Epidemic mumps
	Chickenpox
	Bacterial
	Syphilis
	Septicemia
	Borreliosis (Lyme disease)
	Tuberculosis
	Infective endocarditis
	Protozoal
	Malaria
	Toxoplasmosis
Malignant diseases	Solid tumors
	Lung
	Thymus
	Ovary
	Primary malignant blood diseases
	Myeloid and lymphatic leukemia
	Polycythemia vera
	Myelofibrosis with myeloid metaplasia
	Malignant lymphoproliferative diseases
	Lymphoma and lymphosarcoma
	Mycosis fungoides and Sézary syndrome
	Paraproteinemias
	Monoclonal gammopathy
	Multiple myeloma
Non-malignant blood disorders	Idiopathic thrombocytopenic purpura
	Pernicious anemia
Drugs	Chlorpromazine
	Phenytoin
	Pirimetamine
	Chinidine
	Hydralazine
	Procainamide
	Propranolol
	Interferons
	Quinine
	Amoxicillin
Other conditions	Diabetes mellitus
	Autoimmune thyroiditis (Hashimoto's disease)
	Inflammatory bowel disease (IBD)

cerebral strokes[17]. The prevalence of aPL positivity in children having presented events of ischemic nature in the central nervous system, mostly in the area supplied by the middle cerebral artery, is high, oscillating from 16 to 76%[18]. Leg ulcers, sub-ungueal infarcts, painful necrotizing purpura, splinter hemorrhages and livedo reticularis have been described as possibile cuta-

Table II. Sites involved by thrombotic events and clinical manifestations in the anti-phospholipid syndrome of the pediatric age.

Involved vessels	Clinical manifestations
Veins	
Limbs	Leg swelling, localized edema and pain
Lung	Pulmonary thromboembolism (acute dyspnea)
Skin	Livedo reticularis
Brain	Cephalalgia, papilledema, seizures, hemiplegia
Kidney	Peripheral edema
Liver	Budd-Chiari syndrome
Eye	Amaurosis, abnormal funduscopic examination
Adrenal glands	Addison's disease (adrenal insufficiency)
Arteries	
Brain	Transient ischemic attack (TIA) or ictus
Kidney	
a) large vessels	Renal infarction (pain and hematuria)
b) small vessels	Thrombotic microangiopathy (hypertension)
Limbs	Digital ulcers, ischemia and gangrena
Heart	Myocardial infarction, valvular insufficiency
Liver	Hepatic infarction
Gut	Intestinal occlusion

neous manifestations of APS in the child. Cutaneous ulcers begin more frequently in the pre-tibial face of legs, can be multiple or focal, intensely painful and leave atrophic scars. Livedo reticularis (or livedo racemosa) is a skin manifestation typical of APS: it follows stagnant blood in the superficial venous capillaries dilated of skin of thighs, legs or forearms. The association of livedo reticularis and cerebro-vascular disease (characterized by signs of cerebral ischemia or pseudo-bulbar syndrome) identifies the *Sneddon syndrome*, though it is outstanding in the child. In one third of pediatric patients the possibility of thrombocytopenia and hemolytic anemia is reported; usually the decrease of platelet count is not complicated by hemorrhagic phenomena. The pathogenesis of thrombocytopenia is not clear, though it might originate from the binding of aPL to membrane phospholipids of platelets[19]. About 10-20% of children with APS can present a positive Coombs test, though the inspection of a frank hemolysis and of its consequences is uncommon. The association of thrombocytopenia and hemolytic anemia (which is known as "*Evans syndrome*") is reported in few pediatric cases of APS. Among renal diseases associated with APS in the child we enumerate thrombotic microangiopathy and renal vein thrombosis. Among gastrointestinal manifestations described in children with APS, all secondary to thrombotic events, we point out Budd-Chiari syndrome (caused by the obstruction of hepatic veins or inferior vena cava, with subsequent portal hypertension and ascites), intestinal ischemia, mesenteric and portal vein thrombosis. Aseptic necrosis of femoral head is relatively frequent in the orthopedic workplace and its pathogenesis is depending on the poor blood circulation to the ossification center, due to the hypercoagulable state[20]. Neonatal APS is a clinical entity characterized by neonatal thrombotic disease caused by transplacentally acquired aPL: the rare occurrence of neonatal thrombotic events has been attributed to the lack of the most known "second hit" risk factors in infants and to the low transplacental passage of subclasses of aPL with high pathogenicity. Special concern is needed particularly when dealing with aPL-positive infants who are exposed to other acquired thrombotic risk factors (as central vascular catheters, sepsis, prematurity and congenital heart diseases) and possibly inherited prothrombotic disorders (as antithrombin III, protein C or protein S deficiencies and factor V-Leiden mutation)[21].

Diagnosis of Anti-phospholipid Syndrome

Criteria useful for the diagnosis of APS, pertaining to the clinical setting and laboratory tests, were firstly ratified at Sapporo in 1999 and then modified at Sydney in 2005. APS can be diagnosed only in the presence of at least one clinical criterium and one laboratory criterium. Tables III and IV describe into details the clinical and laboratory criteria which need to be demonstrated to support the diagnosis of APS. In the presence of a thrombotic event, venous or arterious, coagulation assays including aPTT, kaolin clotting time and diluted Russel's viper venom time should be texted in combination with serum ACL and $A\beta_2GpI$ evaluations. In addition aPL positivity must be at "high titre" and verified at least twice

Table III. Clinical criteria for the diagnosis of anti-phospholipid syndrome.

Vascular thrombosis
One or more clinical episodes of venous or arterial thrombosis occurring in any tissue or organ confirmed by ultrasound, echo-Doppler or histopathology examinations

Complications of pregnancy
- One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation
- One or more premature births of morphologically normal neonates at or before the 34th week of gestation (due to severe preeclampsia or severe placental insufficiency)
- Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation (after the exclusion of anatomical and chromosomal abnormalities)

at a distance of 12 weeks to confirm APS diagnosis[22,23]. The occurrence of thrombocytopenia, livedo reticularis and familiarity for autoimmune diseases (in particular for systemic lupus erythematosus) increases the likelihood that APS can be etiologically related to any thrombotic event.

Tables V and VI show the permanent and transitory risks for venous thromboembolism.

Therapeutical/Prophylactic Strategies in the Anti-phospholipid Syndrome

To estimate the risk of thrombotic complications in APS is challenging as well as the questions of which, how long and in what strength anticoagulation is recommended. Different practices have been proposed for treatment and prophylaxis of APS. Initially the management of thrombosis requires the use of thrombolytic drugs (as urokinase at the dose of 4400 IU/kg in bolus, to be continued at the dose of 4400 IU/kg/hour for at least 72 hours) imbricated with intravenous standard heparin (at the dose of 50 IU/kg in bolus, to be continued at the dose of 15-20 IU/kg/hour when the thrombolytic drug is suspended) with the aim of doubling aPTT. Heparin is indeed an efficacious anticoagulant drug which interrupts thrombin activation and strengthens the role of antithrombin III. When the thrombotic process is solving – as an altenative choice to standard heparin – it is possibile to use low-molecular-weight heparin (as enoxaparin at the dose of 100 U/kg every 12 hours), which has a decreased risk of causing hemorrhages[24]. There is unanimous agreement about the necessity of subjecting all children with APS to prophylaxis in order to prevent thrombotic relapses. This requires the administration of oral anticoagulants, originally developed as rat poisons, acting by antagonizing the effect of vitamin K, resulting in reduced hepatic production of active coagulation factors II, VII, IX and X, and hence in pro-

Table IV. Laboratory criteria for the diagnosis of anti-phospholipid syndrome.

Positivity of lupus-like anticoagulant detected in the blood on two or more occasions at least 12 weeks apart

Positivity of anti-cardiolipin IgG and/or IgM antibodies present in moderate or high levels in the blood in two or more occasions at least 12 weeks apart, measured on a standardized ELISA test

Positivity of anti-β_2-glicoprotein I IgG and/or IgM antibodies present in moderate or high levels in the blood in two or more occasions at least 12 weeks apart, measured on a standardized ELISA test

Table V. "Permanent" risk factors for venous thromboembolism.

- Chronic venous insufficiency
- Idiopathic familiar venous thromboembolic disease
- Hyperhomocysteinemia (general prevalence: 2-16%)
- Factor V G1691A (factor V-Leiden) (general prevalence: 5-10%)
- Protein C deficiency (general prevalence: 3%)
- Protein S deficiency (general prevalence: 3%)
- G20210A mutation in prothrombin gene (general prevalence: 2%)
- Antithrombin III deficiency (general prevalence: 1%)
- Chronic myeloproliferative disorders
- Behçet's disease

Table VI. "Transitory" risk factors for venous thromboembolism.

- Surgical interventions
- Traumatic injuries
- Prolonged immobilization
- "Economy class" syndrome
- Infections and pyo-septic diseases
- Pregnancy and puerpery
- Antipsychotic medications
- Oral estroprogestinic formulations
- Nephrotic syndrome
- Systemic vasculitic syndrome

longation of the thromboplastin time expressed as *international normalized ratio* (or INR). Oral anticoagulants as warfarin and acenocoumarol are prescribed at an individualized dose to achieve target INR between 2.0 and 3.0[25,26]. They usually take 48-72 hours to develop a full anticoagulant effect, hence anticoagulation should be commenced with heparin in acute thromboembolism. Heparin is not required when oral anticoagulants are started electively for the prophylaxis of thromboembolism and is contraindicated in cases of severe thrombocytopenia, history of heparin-induced thrombocytopenia, uncontrollable active bleeding or when monitoring of platelets, hematocrit and stool for occult blood is not possible. When warfarin is instituted it is of primary importance to instruct child's parents to avoid excessive consumption of foods containing vitamin K and to instruct carefully the child to avoid activities or sports with excessive contact. In addition it is useful to remind that many drugs may decrease the anticoagulant effects of warfarin, including carbamazepine, phenytoin, barbiturates, cholestyramine, sucralfate, rifampin, spironolactone and obviously vitamin K. Other drugs may increase the anticoagulant effects of warfarin as oral antibiotics, sulfonamides, ketoconazole, miconazole, metronidazole, allopurinol, anabolic steroids, cimetidine and acetaminophen. Bleeding diathesis might be enhanced by the concomitant administration of aspirin, non-steroidal antinflammatory drugs as ibuprofen and naproxen, ticlopidine or clopidogrel and hydroxychloroquine. Duration and intensity of prophylaxis in APS are not definitely well-established: some authors suggest that it must be continued for an indeterminate time, due to the high percentage of new thrombotic events in children having interrupted oral anticoagulant administration already after 6 months. Reproductive counseling is strongly recommended for females of child/bearing age: pregnancies have to be planned so that long-term warfarin can be switched to aspirin and heparin before pregnancy is attempted. The antithrombotic properties of hydroxychloroquine have long been recognized and may be considered in the prophylaxis of patients with systemic lupus erythematosus and a positive aPL test. In patients with "*catastrophic*" APS decisions on treatment have to be proportional to the severity of the clinical picture and can make a use of intensive anticoagulation combined with plasmapheresis, high doses of corticosteroids, cyclophosphamide or intravenous immunoglobulins, although no controlled studies have documented their efficacy[27]. Healthy subjects who occasionally and accidentally result to have aPL in the serum do not need to be treated with any sort of therapy or prophylaxis[28].

With appropriate medication and lifestyle modifications most children with primary APS can lead normal lives and reach adulthood without problems. Only a minority of children with secondary APS displays a severe course, often leading to significant morbidity, though this might also be influenced by the underlying rheumatologic or autoimmune condition.

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