TABLE 379-1 CLASSIFICATION AND NOMENCLATURE OF ANTIPHOSPHOLIPID ANTIBODIES

Name	Assay for their Detection	Comments
Antibodies against cardiolipin (aCL)	Enzyme-linked immunosorbent assay (ELISA) using as antigen cardiolipin (CL), a negatively charged phospholipid	aCL from patients with APS recognize β2GPI existing in the human serum as well as in bovine serum, which is used to block the nonspecific bindings sites on the ELISA plate. CL simply stabilizes β2GPI at high concentration on the polystyrene surface.
Antibodies against β2GPI (anti-β2GPI)	ELISA using as antigen affinity purified or recombinant β2GPI in the absence of PL	Antibodies recognize β2GPI bound in the absence of CL to an oxidized polystyrene surface, where oxygen atoms in the moieties C-O or C=O were introduced by γ-irradiation.
Lupus anticoagulant (LA)	Activated partial thromboplastin time (aPTT) Kaolin clotting time (KCT) Dilute Russel viper venom test (DRVVT)	Antibodies recognize β2GPI or prothrombin (PT) and elongate aPTT, implying that they interfere with the generation of thrombin by prothrombin. Prolongation of the clotting times is an in vitro phenomenon, and LA induces thromboses in vivo.

Abbreviations: APL, antiphospholipid syndrome; β2GPI, β2 glycoprotein I; PL, phospholipid.

(BFP-STS) and Venereal Disease Research Laboratory (VDRL) tests. APS may occur alone (primary) or in association with any other autoimmune disease (secondary). Catastrophic APS (CAPS) is defined as a rapidly progressive thromboembolic disease involving simultaneously three or more organs, organ systems, or tissues leading to corresponding functional defects.

EPIDEMIOLOGY

Anti-PL (aPL)-binding plasma protein antibodies occur in 1–5% of the general population. Their prevalence increases with age; however, it is questionable whether they induce thrombotic events in elderly individuals. One-third of patients with systemic lupus erythematosus (SLE) (Chap. 378) possess these antibodies, whereas their prevalence in other autoimmune connective tissue disorders, such as systemic sclerosis (scleroderma), Sjögren's syndrome, dermatomyositis, rheumatoid arthritis, and early undifferentiated connective tissue disease, ranges from 6 to 15%. One-third of aPL-positive individuals experience thrombotic events or pregnancy morbidity.

PATHOGENESIS

The trigger for the induction of antibodies to PL-binding proteins is not known. However infections, oxidative stress, major physical stresses such as surgery, and discontinuation of anticoagulant treatment may induce the exacerbation of the disease. Experimental data have shown that these phenomena are induced via (1) conformational changes of β2GPI either complexed with microbial antigens or dimerization through interaction with endothelial cell surface receptor annexin 2/TLR4, the platelet receptors apolipoprotein E receptor 2′ (apoER2′) and/or GPIb/IX/V receptor, and/or the chemokine platelet factor 4 (PF4); or (2) impaired defensive mechanisms such as reduced generation of endothelial nitric oxide synthase. Adherence of β2GPI to apoER2′, GPIb/IX/V receptor, and/or PF4 induces activation of endothelial cells, platelets, and monocytes. This process activates downstream pathways such as p38 mitogen-activated protein (p38 MAP) kinase and nuclear factor (NF)-κB, leading to the following events: secretion of proinflammatory cytokines, such as interleukin (IL) 1, IL-6, and IL-8; the expression of adhesion molecules; inhibition of cell-surface plasminogen activation; and expression of tissue factor. The above events change the phenotype of these cells to a prothrombotic form. In addition, anti-β2GPI antibodies induce fetal injury in mice through complement activation, as shown by the evidence that C4-deficient mice were protected from fetal injury.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Clinical manifestations represent mainly a direct or indirect expression of venous or arterial thrombosis and/or pregnancy morbidity (Table 379-2). Clinical features associated with venous thrombosis are superficial and deep vein thrombosis, cerebral venous thrombosis, signs and symptoms of intracranial hypertension, retinal vein thrombosis, pulmonary emboli, pulmonary arterial hypertension, and Budd-Chiari syndrome. Livedo reticularis consists of a mottled reticular vascular pattern that appears as a lace-like, purplish discoloration of the skin. It is probably caused by swelling of the venules owing to obstruction of capillaries by thrombi. This clinical manifestation correlates with vascular lesions such as those in the central nervous system as well as aseptic bone necrosis. Arterial thrombosis is manifested as migraines, cognitive dysfunction, transient ischemic attacks, stroke, myocardial infarction, arterial thrombosis of upper and lower

TABLE 379-2 CLINICAL FEATURES OF ANTIPHOSPHOLIPID SYNDROME

Manifestation	%
Venous Thrombosis and Related Consequences	
Deep vein thrombosis	39
Livedo reticularis	24
Pulmonary embolism	14
Superficial thrombophlebitis	12
Thrombosis in various other sites	11
Arterial Thrombosis and Related Consequences	
Stroke	20
Cardiac valve thickening/dysfunction and/or Libman-Sacks vegetations	14
Transient ischemic attack	11
Myocardial ischemia (infarction or angina) and coronary bypass thrombosis	10
Leg ulcers and/or digital gangrene	9
Arterial thrombosis in the extremities	7
Retinal artery thrombosis/amaurosis fugax	7
Ischemia of visceral organs or avascular necrosis of bone	6
Multi-infarct dementia	3
Neurologic Manifestations of Uncertain Etiology	
Migraine	20
Epilepsy	7
Chorea	1
Cerebellar ataxia	1
Transverse myelopathy	0.5
Renal Manifestations Due to Various Reasons (Renal Artery/Renal Vein/Glomerular Thrombosis, Fibrous Intima Hyperplasia)	3
Osteoarticular Manifestations	
Arthralgia	39
Arthritis	27
Obstetric Manifestations (Referred to the Number of Pregnancies)	
Preeclampsia	10
Eclampsia	4
Fetal Manifestations (Referred to the Number of Pregnancies)	
Early fetal loss (<10 weeks)	35
Late fetal loss (≥10 weeks)	17
Premature birth among the live births	11
Hematologic Manifestations	
Thrombocytopenia	30
Autoimmune hemolytic anemia	10

Source: Adapted from R Cervera et al: Arthritis Rheum 46:1019, 2002.