RECENT ADVANCES IN ANTIPHOSPHOLIPID SYNDROME: PATHOGENESIS, NEW CRITERIA AND MANAGEMENT

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بسم الله الرحمن الرحيم

(قالوا سبحانك لا علم لنا إلا ما

علمتنا إنك أنت العليم الحكيم)

صدق الله العظيم

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Historical landmarks:

The story begun in ١٩٠٦**,** when **Von Wasserman** described complement fixation test for syphilis. In his original report, extracts of beef heart were used as antigen. Antibody in syphilitic sera was called regain.

During ١٩٣٠s, millions of serologic test for syphilis (STS) especially VDRL were performed on military inductees with clinical observation that ٥٠٪ of military personnel with positive VDRL were found to have no clinical features of syphilis. This was a biological false positive STS (BFP-STS) which was seen also in premarital testing **(Triplett, ٢٠٠٠).**

Margaret Pangborn (١٩٤١) found that extracts of beef heart contained PL and identified it as the antigenic component in regain test and latter called cardiolipin (CL).

Two apparently unrelated papers appeared**, Conley and Hartman (١٩٥٢)** found prolonged prothrombin time and BFP-STS in patients of hemorrhagic disorder while **Moore and Mohr (١٩٥٢)** divided BFP-STS into acute BFP-STS that follow infection and chronic BFP-STS in which positive results persist more than ٦ months and associated with high incidence of

autoimmune diseases. In addition, they observed high incidence of BFP-STS in young women with thrombocytosis as well as thrombosis.

Moor and Lutz (١٩٥٥) observed that some women with BFP-STS developed SLE after an enough time and three of ٢١ lupus patient had had major unexplained thrombophlebitis.

Laurel and Nelson (١٩٥٧) found that the anticoagulant was attributable to BFP-STS and both were associated with obstetric complication and thrombocytopenia while **Bowie (١٩٦٣)** reported frequent occurrence of thromboses rather than bleeding in SLE patients who had this inhibitor of coagulation.

Again, **Johansson and Lassus (١٩٧٤)** confirmed the concurrent finding of BFP-STS and circulating anticoagulant that was termed lupus anticoagulant (LA) by **Fein stein and Rapaport (١٩٧٧).**

Thiagarajan and colleagues (١٩٨٠) found that at least some of LA was an aPL and are responsible for in vitro anticoagulant effect and BFP-STS and in the same year **Soulier and Boffa** recorded occurrence of recurrent abortion, thromboses and circulating anticoagulant.

Nigel Harris (١٩٨٣) developed solid phase radioimmunoassay (RIA) and later **Koike and colleagues (١٩٨٤)** developed enzyme-linked immunosorbent assays (ELISA) to quantitate aCL. This enabled **Graham Hughes (١٩٨٥)** to propose a new clinical entity (anticardiolipin syndrome) and **Loizou** to develope ELISA using CL Antigen.

In ١٩٩٠ at the antiphospholipid meeting in Sirmione, Italy, **Monica Galli** proposed that antibodies detected by ELISA tests with CL as antigen were not directed to the PL but to a protein cofactor present in the bovine serum used to block the plates. **McNeil and colleagues** determined that the protein cofactor was ß٢GPI, which had natural anticoagulant properties and high affinity for anionic molecules such as CL. Moreover, as noted by **Matsuura and colleagues**, pathogenic antibodies can be distinguished from those present in infectious disease. The pathogenic antibodies require the presence of bovine serum with such cofactor, the infectious antibodies do not. The corresponding articles were published that same year (١٩٩٠).

At a ß٢GPI symposium in Milan in ١٩٩٢**, Shoenfeld and Meroni** described the presence of anti-ß٢GPI in a group of patients with primary APS. That these antibodies may have the

most important role in the causation of the APS, particularly its thrombotic component, was evidenced by their systematic fall at the time of thrombosis, as found by **Gómez-Pacheco and coworkers (١٩٩٩).**

Matsuura and Koike (١٩٩٥) revealed that the so-called aCL antibodies could bind to ß٢GPI in the absence of CL if the ELISA plates were oxidized by irradiation. This procedure was considered by **Roubey and coworkers (١٩٩٥)** to cause higher antigen density and permit bivalent binding. **Cabiedes and colleagues (١٩٩٥)** found that manifestations of APS associated more strongly with anti-ß٢GPI determined in non-irradiated plates versus those with aCL, and **Alarcon-Segovia and Cabral (١٩٩٦)** subsequently described groups of patients with clinical manifestations of APS who had persistently negative aCL when studied in conventional assays, but persistently positive anti-ß٢GPI determined in non-irradiated plates.

Finally, the diagnosis of APS is based on the modified clinical and laboratory classification criteria as proposed by an international workshop group after the International Symposium on aPL, in Sapporo, Japan **(Marai et al., ٢٠٠٤)**.

Epidemiology:

aCL antibodies are seen in the general population. Prevalence is ٢ to ٤٪, and they are usually low in titer and more common in the elderly. In contrast, about one-third of SLE patients are aCL positive. LA prevalence is less than ١٪ in the general population, and about ١٥٪ in SLE patients. The strength of the association between aPL and thrombosis varies, depending on both the aPL tested and the populations studied. Titer and isotype are important: immunoglobulin Ig G aCL is more strongly associated with clinical events than is IgM aCL, and the risk of thrombosis increases with higher titers. IgA aCL and low titers of IgG and IgM aCL are less frequently associated with complications **(Godfrey and D'Cruze, ٢٠٠٠).**

APL account for a significant proportion of thromboses in the general population: approximately ٥٠٪ of stroke patients younger than age ٥٠, and up to ٢٠٪ of idiopathic deep venous thrombosis (DVT) patients are aPL positive. ACL are predictive of DVT and pulmonary embolism in the general population. In a nested case-control subset of the Physicians Health Study, a positive aCL test at study onset was associated with subsequent development of DVT and pulmonary embolism. Risk of thrombosis in lupus

patients is significant; there is a ٥٠٪ chance of thrombosis over ٢٠ years for LA-positive SLE patients, and a ٥٢٪ chance of developing any APS complication over ١٠ years for aPL-positive lupus patients **(Sammaritano, ٢٠٠٥).** Women with pregnancy events alone have a high likelihood of developing thrombosis in later years. **Erkan and colleages** have shown a thrombosis rate of ٦٠٪ by ١٠ years after delivery (**Erkan et al., ٢٠٠١**).

The presence of additional pro-thrombotic risk factors in aPL-positive individuals likely influences thrombosis risk. In the currently accepted "second-hit" hypothesis, a second trigger event - such as cigarette smoking, oral contraceptives, surgical procedures, prolonged immobilization, or a genetic pro-thrombotic state may increase the likelihood of an aPL-positive patient developing a vascular event **(Sammaritano, ٢٠٠٥).**

The Montpellier study included ١٠١٤ patients admitted to the general medical floor for a variety of reasons and were assessed for aCL. Of the patients tested, ٧٫١٪ were positive for at least one idiotype. However, only ٢٨٪ were determined to have clinical manifestations of APS, indicating a false positive incidence of ٥٫١٪**.** In another study, ٥٥٢ healthy blood donors were screened for aCL IgG, IgM idiotype antibodies, and LA **(Bick, ٢٠٠١)**.

٦,٥٪ had the IgG idiotype, ٩,٤% had IgM idiotype aCL, and ٥ donors had both idiotypes. No donor was positive for LA. No thrombotic complications were noted in aCL-positive donors after ١٢ months. However, nine aCL–positive donors had a family history of thrombosis, and three of the aCL–positive donors had a history of unexplained miscarriage. In a survey of ١٠٠ consecutive patients with DVT or pulmonary embolism, ٢٤٪ were found to have aCL. These findings suggest that aCL are common in patients with unexplained DVT or pulmonary embolism; therefore any patient with unexplained thrombosis should be evaluated for the presence of aPL **(Gezer, ٢٠٠٣).**

The Prevalence of the APS in patients with primary systemic vasculitis (PSV) and the prevalence of patients with positive aCL and/or the LA who do not fulfill the classification criteria for APS (Sapporo criteria) were studied. ١٤٤ patients with PSV were assessed for features of the APS and presence of aPL., ٢٥ had positive aCL or LA on at least one occasion, representing a point prevalence of ١٧٪. Of these, nine had definite APS and a further four patients had clinical and serological features of APS, although insufficient to satisfy the Sapporo criteria. Twelve had only positive aPL **(Rees et al, ٢٠٠٦).**