The history of antiphospholipid syndrome

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SUMMARY

Antiphospholipid Syndrome (APS) is an autoimmune disease which was defined in the early 1980s. The principal features include thromboembolic events and/or pregnancy losses in association with antiphospholipid antibodies (aPL). As an historical note, the full-blown picture of the syndrome resembles the illness suffered by Anne Stuart, Queen of England in the XVIII century, whose repeated miscarriages caused the end of the royal Stuart line and the Hanoverian succession.

The identification of aPL started in the early XX century and was linked to the introduction of the serological test for the diagnosis of syphilis. This involves a reaction between an antibody (reagin) and a phospholipid antigen derived from bovine heart (cardiolipin). Later on, it was observed that not all subjects with a positive test had syphilis, and that the so called "false positive reaction" was often reported in patients with systemic lupus erythematosus.

Different tests for the identification of aPL were subsequently developed: first lupus anticoagulant (1971) and then immunoassays for anticardiolipin (1983) and anti-beta2 glycoprotein I (1990) antibodies. In the same period the association between the presence of circulating aPL and thrombotic and obstetric events was established, both in patients with autoimmune diseases and in otherwise healthy subjects, leading to the identification of APS as a distinct autoimmune disease. This has allowed better diagnosis and more targeted treatment for many patients.

Key words: *Anticardiolipin antibodies, Anti beta2glycoprotein I antibodies, Lupus anticoagulant, Antiphospholipid Syndrome, Systemic Lupus Erythematosus.*

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INTRODUCTION

The history of the antiphospholipid syndrome (APS) is a complex network of laboratory and clinical observations representing one of the best examples of so called "translational medicine".

The full-blown definition of a new disease including thromboembolic events and/or pregnancy losses in the presence of antiphospholipid antibodies (aPL) was established in the early 1980s. This important discovery became possible because of earlier work and led directly to numerous clinical and experimental observations. However, only after the 1980s did the medical community understand the pathogenic potential of aPL and awareness of APS as a systemic autoimmune disease became part of common practice. Interest in APS increased rapidly, chiefly due to the multidisciplinary involvement of physicians. Hematologists, rheumatologists, gynecologists and internal medicine specialists were active players from the early days, while others such as cardiologists, neurologists, dermatologists etc., became involved following clinical observations of widespread organ involvement. At the end of the last century APS was included in the textbooks of medicine and rheumatology and this was appropriate because, as was reported, "…there are two new diseases in the late 20th century: AIDS and APS" (1).

THE HISTORICAL FIRST CLINICAL CASE

Long before the invention of complement-fixing tests, *in vitro* clotting studies and immunoassays, patients were being described

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with features that we would now recognize as characteristic of antiphospholipid syndrome. One example is an extremely prominent English lady who died of a stroke in 1714 at the age of 49. She had had a long medical history. Most striking was her obstetric story. In 1684 her first pregnancy ended in a stillbirth. In the next two years two daughters were born, but they tragically died from smallpox in 1687. After three miscarriages she gave birth to a son who probably had hydrocephalus and subsequently died at the age of 11. After this, two children were born, both of whom lived for less than a day. There followed a succession of eight pregnancies, all of which miscarried. There were no further live births. Thus, out of a total of 17 pregnancies 11 resulted in miscarriage, with additionally one stillbirth and two neonatal deaths. The patient had several other longstanding medical problems. They included colour changes in the peripheries which we would now describe as Raynaud's phenomenon. She had widespread migratory joint pains; some of these were in large joints and may have related to obesity, but she also had recurrent small joint pain. There was a facial rash which could be disfiguring. She may have had at least one grand mal fit. Towards the end of her life, she suffered from "dropsy", which may be interpreted as fluid retention. The patient was Anne Stuart, who was born in 1665, and became Queen of England, Scotland and Ireland in 1702. We cannot of course know for certain what modern diagnostic labels would be given to Queen Anne's ailments. There are many possibilities. However, one condition that could provide a unifying diagnosis for most if not all of her problems is systemic lupus erythematosus (SLE) with associated APS (2). SLE could have caused migratory joint pains and facial rash; and APS could have been responsible for her multiple miscarriages, as well as Raynaud's phenomenon, seizure and stroke.

Queen Anne's disastrous obstetric history was not just a personal tragedy but had a major dynastic consequence. Since she had no surviving children, and there was no close heir, the royal Stuart line came to an end at her death. The Crown passed to a cousin, George, Elector of Hanover, who came over from Germany to become King George I. It is from him that all subsequent members of the British Royal Family have descended. Clearly the diagnosis for Queen Anne's condition must remain speculative. However, given the overall clinical picture, APS does appear to be a very strong candidate to explain the obstetric history. If Queen Anne did indeed have APS, it can be regarded as the principal cause for the Hanoverian succession and a major development in British history.

Figure 1 - Queen Anne's portrait by Charles Boit enamel on copper, circa 1705 © National Portrait Gallery, London.

FROM 1900 TO 1980

It was in 1906 that Wassermann described the serological reaction for the diagnosis of syphilis (3). This used an alcoholic cell extract, rich in phospholipids. The substance responsible for the reaction was called "reagin". Originally the reaction was a complement fixation test, subsequently modified as a flocculation test. This modification was later used to set up the Venereal Disease Research Laboratory test (VDRL), a rapid flocculation test which is still used diagnostically (4).

It was only several years later, in 1941, that the target antigen of reagin was character-

ized as a phospholipid derived from bovine heart and therefore called cardiolipin (5). With the use of the tests done on large populations such as soldiers during the Second World War, it became clear that not all subjects with positive results were affected by syphilis (6). As a consequence, tests more specific for syphilis were introduced such as the Treponema Pallidum Immobilization test (TPI) and the Fluorescent Treponema Protein Absorption test (FTA-ABS). The use of these specific tests focused attention on why some patients with different infective and non-infective diseases displayed a so called "biological false positive test for syphilis" (BFP-STS). In the 1950s BFP-STS was also described in patients with SLE (7).

Around the same time two SLE patients were reported who developed hemorrhages due to a peculiar anticoagulant activity characterized by a prolonged prothrombin-thrombin conversion (8). This anticoagulant was found in the blood of other patients and not always associated with bleeding problems. A few years later, it was observed that the presence of this anticoagulant was associated with BFP-STS (9) and that it could be absorbed by phospholipids (10).

Finally in the 1970s this anticoagulant activity was demonstrated to be due to an acquired immunoglobulin (IgG or IgM) partially inhibited by the addition of phospholipids or platelets and called "lupus anticoagulant" (LA) (11).

The clinical studies on SLE performed in the Mayo Clinic in the 1960s described the presence of peripheral arterial occlusion, Raynaud's phenomenon, chronic leg ulcers, livedo reticularis, and recurrent thrombophlebitis often associated with circulating anticoagulants as part of the natural history of the disease (12, 13).

Although the first report linking circulating anticoagulants to recurrent pregnancy losses goes back to 1954 (14), only in the 1970s was LA clearly associated with fetal loss in women with placental pathology (vasculopathy, infarctions etc.). Interestingly these events were also reported in apparently healthy women (15, 16). Finally, in 1980, Soulier and Boffa described three otherwise healthy young women with circulating anti-thromboplastin anticoagulant who suffered mid-pregnancy miscarriages and thrombo-embolic episodes (17).

FROM 1980

Following on directly from the seminal work of Carreras and Vermylen, the association of LA with recurrent miscarriages, intrauterine fetal death and thrombosis was confirmed by several case reports in the early 1980s (18, 19).

However, the establishment of a new syndrome was primarily due to G.R.V. Hughes, who first described the multidisciplinary aspects of the disease linked to the presence not only of LA but also anticardiolipin antibodies (aCL) (20). He focused on the close relationship between connective tissue diseases and this new condition which was characterized by "thrombosis, abortions and cerebral disease" and often associated with a generally mild thrombocytopenia. The autoimmune nature of the syndrome was supported at this time by the observation that corticosteroid administered during pregnancy to women with recurrent miscarriages and LA could abolish LA activity and allow a successful outcome (21).

The description of an immunoassay for aCL by N. Harris was the real driver for the establishment of this new disease (22). The direct detection of aCL was performed by a completely different technique from the LA test, initially a radioimmunoassay, from which was soon developed an enzyme linked immunoassay (ELISA). This enabled the simultaneous testing of large numbers of samples, allowing physicians of all over the world to study their patient cohorts, make the diagnosis and start effective treatments. These were based on anticoagulant and/or antiaggregant drugs. In the same period, Harris also observed that the antibodies were not only targeting cardiolipin but were directed against the broad family of negatively-charged phospholipids. The name of the new disease was therefore soon changed from "anticardiolipin syndrome" to "antiphospholipid syndrome" (APS) (23).

At this stage most of the patients in whom

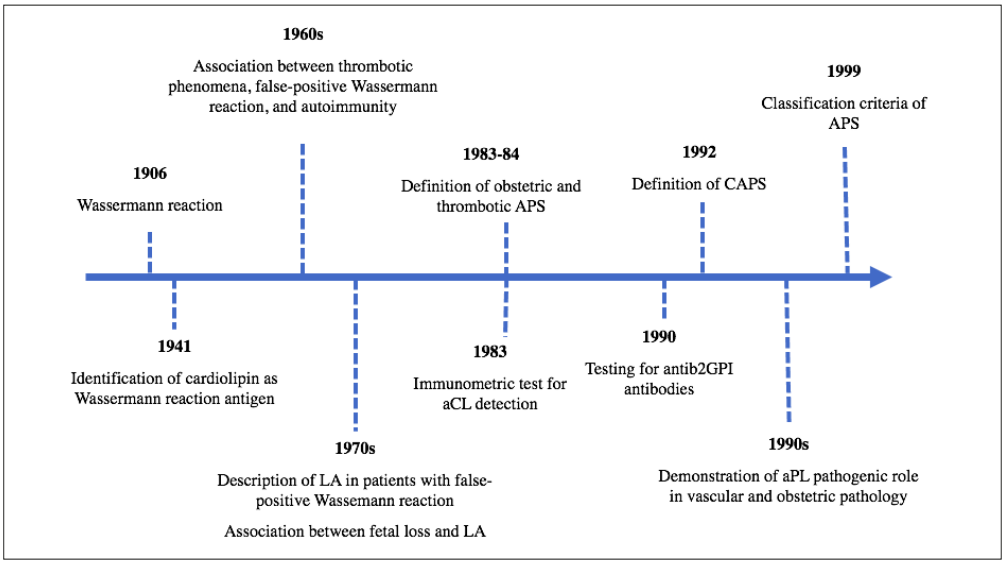

Figure 2 - Chart summarizing the milestones of the history of antiphospholipid antibodies syndrome.

APS had been described had SLE or a similar autoimmune condition. However, it soon became apparent that APS could exist by itself in a primary form. This was important in establishing the condition as an independent entity (24, 25). In 1990, three groups simultaneously showed that in the majority of patients the target of aPL was not the phospholipid molecule itself but a protein present in normal plasma which binds negatively charged phospholipids, beta2 glycoprotein I (b2GPI) (26-28). This finding allowed the development of a new test, the anti-b2GPI assay. The results were closely related to those of LA and aCL assays, although anti-b2GPI appeared to be more prevalent in patients with autoimmune diseases and less in infective conditions (where aCL assays were more frequently positive) (29).

The 1990s saw another important milestone in APS history: the first clear evidence that aPL are responsible for the disease. This came from animal models of APS, both spontaneous, in lupus prone mice (30), and induced, in healthy animals injected with purified aCL. This latter type of model was initially created in BALB/c mice by W. Branch in US (31). The concept was developed with some modifications in ICR outbred normal mice by Y. Shoenfeld (32) and this model proved to be the most widely used in the following years. All of the above models used pregnant animals to show that aPL can directly impair pregnancy outcome. By contrast, a model using an *in vivo* thrombosis technique was used by S. Pierangeli to demonstrate that aPL have a direct effect on thrombus formation (33). Subsequently, similar models were used to look for strongly pathogenic aPL: different polyclonal and monoclonal antibodies were studied including those directed to different domains on the b2GPI molecule. Some of these experiments were performed in the presence or absence of complement which confirmed its role in aPL-mediated damage (34).

Running parallel to the animal model experiments, a large body of *in vitro* work focused on the effects of aPL on cells. In a series of seminal papers P.L. Meroni and S. Pierangeli clearly showed the complex interplay between endothelial cells and aPL, and their important contribution to the vascular manifestations of APS (35). A few years later the same international group showed evidence that aPL could impair trophoblast function and therefore cause pregnancy loss (36).

In the 1990s another piece was added to the APS puzzle. R. Asherson described the catastrophic APS (CAPS) (37). This is a severe

form of APS characterized by multiple organ failure occurring in few days with histopathological evidence of small vessel occlusions. The definition of CAPS allowed the identification of a group of very severely affected patients that need to be managed with aggressive therapeutic strategies.

Since 2000 a considerable amount of further work on APS has been done; and of course still more is needed. Among the many topics of current interest are: risk evaluation, including antibody profile and standardization; the evaluation and measurement of damage that can be of help to understand the long-term outcome for patients; and possible new treatments such as statins and immunosuppressive drugs. However, even if our research agendas are still full, most workers in the field would probably agree that the principal elements of this new disease were fully described in the final two decades of the last century.

International collaboration has been an important element in this story. From an early stage this was formalized through the institution of International Workshops. Starting in 1984 and repeated each two years, these were able to link the expertise of coagulation experts, gynecologists, rheumatologists, clinical immunologists and internists. They helped to define the true nature of the disease and enabled agreement on classification criteria. These were first published in 1999 (38), were subsequently modified in 2006 (39) and are currently undergoing revision (40). The International Workshops were not the only cooperative initiatives. Examples are the aPL European Forum, which described the first large APS cohort including 1000 patients (41), and APS ACTION, which includes an international registry connected to a biobank (42). Recently the European network of rare diseases has included APS as one of its topics.

ANTIPHOSPHOLIPID SYNDROME IN THE WORLD: A REVOLUTION IN FAVOR OF WOMEN

While many questions about the treatment and prediction of vascular events are still to be answered, the definition of APS caused a true revolution in women's health. Patients with a diagnosis of systemic autoimmune disease or with some clinical or serological autoimmune features had often reported a poor obstetric history that in many instances prevented them from having a happy family life. As physicians became aware of APS many of these patients were found to be aPL-positive, as were a number of women without any disease but suffering unexplained repeated pregnancy loss. Treatment with antiaggregant and anticoagulant drugs turned out to be remarkably effective in the majority of cases. This has really changed the life of many families all over the world; and, had it been available, it might also have changed the course of British history many years ago.

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