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1. Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, and SCDU Nephrology and Dialysis, S. Giovanni Bosco Hospital and University of Turin

2. School of Specialization of Clinical Pathology, Department of Clinical and Biological Sciences, University of Turin, Italy

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Introduction

Antiphospholipid syndrome (APS, also known as Hughes Syndrome) is an autoimmune condition characterized by the occurrence of thrombotic events and/or pregnancy morbidity in individuals found to be persistently positive for antiphospholipid antibodies (aPL). APS is also known as the most common among the various forms of acquired thrombophilia with the peculiarity of potentially involving both arteries and/or veins at any level.

The aim of this article is to provide an overview of the thrombotic manifestations of APS and the available therapeutic options.

The GP's curriculum and Thrombotic antiphospholipid syndrome (Hughes Syndrome):

Clinical Example: Care of people with unprovoked/cryptogenic thrombosis requires that GPs should:

- Know the epidemiology of common and/or important thrombophilias such as antiphospholipid syndrome
- Know the indications for antiphospholipid antibody testing and indications for referral to a specialist for the management of high risk patients who require special monitoring
- Carry out laboratory testing to rule out any other thrombophilias
- Demonstrate an understanding of the relevance of management and the effective use of special investigations such as e.g routine echocardiography and routine microscopic examination of the urine sediment), especially when considering the possible “extra-criteria” clinical manifestations of antiphospholipid syndrome .
- Recognize that thrombosis affects a young population of patients affected by antiphospholipid syndrome and that, especially arterial thrombosis, can have a strong impact on the patients’ quality of life, as it is the most severe and life-threatening manifestation of the disease

Key Points (5-6)

1.The antiphospholipid syndrome is recognized as the most common acquired thrombophilia

2.Thrombotic events in antiphospholipid syndrome can affect the venous and the arterial system

3.While deep vein thrombosis represent the most common thrombotic manifestation of antiphospholipid syndrome, the most common neurological manifestation is ischaemic stroke.

4.Treatment in APS is mainly based on indefinite anticoagulation with vitamin K antagonists or, occasionally, low molecular weight heparin.

5.More recently, the use of direct oral anticoagulants has been considered: Rivaroxaban might be an effective alternative in patients with APS and previous venous thromboembolism with a low risk antiphospholipid antibody profile.

Main Section

1. Thrombosis

The presence of antiphospholipid antibodies (aPL) is an important risk factor for developing thrombotic manifestations. In individuals with aPL, single or multiple vessel thromboses may appear in any site (venous, arterial and/or capillary). The time interval between thrombotic manifestations of the disease may vary from days to years. This variability results in the wide spectrum of clinical presentations which may involve various systems [1].

Venous thromboembolism, and especially deep vein thrombosis (DVT) of the lower limbs, is the most frequent manifestation of APS with a prevalence of approximately 39% among the patients participating in the Euro-Phospholipid Project[2]. Although arterial thrombosis is less common, it may be more severe and life-threatening, usually presenting as stroke (20%) or as a transient ischaemic attack (TIA) (11%) (Box 1). It must also be acknowledged that the recurrence rate of thrombotic events in untreated patients after unprovoked first events is high and ranges from 19 to 29% per year[3][4].

1.1 Neurologic manifestations

Ischaemic stroke involving the territory of the middle cerebral artery is the most common and severe neurological manifestation associated with APS[2]. A wide spectrum of 'non-criteria' neurological manifestations however have been associated with antiphospholipid antibodies, including cognitive dysfunction (due to multiple cerebral small vessel thromboses), untreatable headaches, migraine, epilepsy, chorea, ocular manifestations such as amaurosis fugax, and retinal vessel thrombosis[5][6].

Among the neurological manifestations, epilepsy can be observed in patients with aPL, and it has strongly associated with previous strokes and TIA, as well as with the presence of systemic lupus erythematosus (SLE), valvulopathy and livedo reticularis [7][8,9].

1.2 Renal manifestations

Thrombotic manifestations are the main cause of renal involvement in APS. Thrombotic microangiopathy caused by antiphospholipid antibodies may manifest through the slow, silent onset of haematuria, proteinuria (ranging from mild to nephrotic levels) and renal insufficiency, or it may develop acutely and present with acute renal failure and hypertension[10][11]. The diagnosis should be supported by a kidney biopsy [12][13][14], especially in SLE patients in whom antiphospholipid antibody-associated nephropathy may be isolated or concomitant with SLE nephritis.

1.3 Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome (CAPS) is a rare, life-threatening form of APS occurring in less than 1% of all subjects with aPL. It is defined as intravascular thrombosis affecting three or more organs, systems and/or tissues, all of

which either develop simultaneously or in less than one week and that have histologically confirmed small vessel occlusion[15][16]. Although CAPS usually involves small vessel thromboses, large vessels are often occluded as well. The prevalence of CAPS is slightly higher in patients with APS alone (60%), as compared to APS associated with other systemic autoimmune diseases (40%) [17]. Infections are the most common precipitating factor of CAPS (49%). The most commonly involved systems in CAPS include renal (73%), pulmonary (60%), cerebral (56%), cardiac (50%), and skin (47%). Among laboratory features, thrombocytopenia is the most frequent (67%), followed by schistocytes (22%). The 12-year mortality rate is 37% in the CAPS Registry, while a higher mortality of 48% is found in SLE patients secondary to severe cardiac and brain involvement.

1.4 Cardiac manifestations

When referring to cardiac involvement, myocardial infarction, and less frequently, intracardiac thrombi are the most common thrombotic manifestations. Myocardial ischaemic events may result from coronary thrombosis without underlying atherosclerosis or accelerated atherosclerosis of the coronary arteries, or microvascular injury. Myocardial infarction is seen in approximately 5.5% of APS registry patients [18–20]. Cardiac features also include valve lesions, accelerated atherosclerosis, pulmonary hypertension, cardiomyopathy and diastolic dysfunction[6]. Cardiac valve abnormalities are seen in 30-50% of APS patients and often include valve thickening and regurgitations, although valve vegetations ("Libman Sacks endocarditis") and valve stenosis can also be observed [21,22]. The mitral valve is most commonly involved, followed by the aortic valve. Valve damage is more frequent in patients with APS associated with other autoimmune diseases [23].

1.5 Pulmonary manifestations

Pulmonary embolism (PE) and infarction constitute the most frequent pulmonary manifestations of APS, affecting approximately 14% of APS patients[2]. Additional pulmonary expressions include pulmonary hypertension, acute respiratory distress syndrome, intra-alveolar haemorrhage, and they may be associated with another autoimmune disease, i.e., fibrosing alveolitis [24].

2. Management

2.1 Management of thrombosis

Primary thromboprophylaxis is a term used to describe the prevention of thrombosis in subjects without previous clots, while secondary thromboprophylaxis describes the prevention of clots in patients who have already had a thrombosis. To date, preventing thrombotic manifestations and recurrences remains one of the greatest challenges in APS (Box 2).

Conventional management of cardiovascular risk factors is key in primary prevention, and the use of low-dose aspirin (LDA) should be limited to individuals at very high-risk of developing clinical manifestations of the disease and in those patients with aPL and concomitant autoimmune diseases[25]. Secondary thromboprophylaxis is based on anticoagulation, mainly with vitamin K antagonists[25].

2.2 Primary thromboprophylaxis

The presence of antiphospholipid antibodies in asymptomatic individuals is a risk factor for thrombosis. For example, a study assessing the risk of stroke in women aged <50 years showed that 17% were positive for lupus anticoagulant (LA) compared to 0.7% in the control group (OR 43.1) [26]. Positivity for lupus anticoagulant combined with oral contraceptives or smoking increased the risk further (OR 201.0 and 87.0, respectively) [26]. Antiphospholipid antibodies are currently unmodifiable, so modifying conventional cardiovascular risk factors in APS patients seems logical despite the lack of clinical trials [27,28]. Modifications include stopping smoking, and addressing hypertension, obesity and hyperlipidaemia.

Erkan *et al.* conducted a randomized clinical trial (RCT) of LDA versus placebo [29] in subjects with isolated antiphospholipid antibodies, but the incidence rate of acute thrombosis in the placebo arm was 0 per 100 patient-years and so the trial was underpowered to detect any effect of LDA[134]. Eleven observational studies involving 1,208 antiphospholipid antibody-positive patients having 139 thrombotic events treated with LDA were combined in a recent meta-analysis by Arnauld*et al.,* which suggested that treating individuals who have isolated antiphospholipid antibodies or APS with LDA is associated with a 50% decrease in the risk of thrombosis occurrence [30]. However, LDA treatment was associated with an increased bleeding risk. In a meta-analysis involving more than 95,000 individuals from six RCTs, LDA intake increased the risk of a major bleed from 0.007% to 0.10% per year [31]. Age >65, male sex, diabetes mellitus and hypertension were associated with an increased risk of bleeding[31].

Hydroxychloroquine has been suggested as an alternative to LDA in the setting of primary prevention in individuals with antiphospholipid antibodies. However, despite recent *in vitro* evidence [32,33], hydroxychloroquine is used in the clinical setting based on empiric evidence and no rigorous RCTs have been carried out (ClinicalTrials.gov Identifier: NCT01784523).

Current treatment recommendations for asymptomatic individuals with persistent antiphospholipid antibodies are based on an individual basis and on the presence of additional cardiovascular risk factors [25]. High risk individuals (those with high titres, triple positivity or additional cardiovascular risk factors) should be evaluated for primary prevention with LDA or hydroxychloroquine[25].

Patients with previous obstetric complications associated with antiphospholipid antibodies are at higher risk for future

thrombosis than the general population. A retrospective cohort showed that subjects with obstetric APS developed a thrombotic event later on, at a rate of 7.4 per 100 patient-years in the non-treated group and 1.3 per 100 patient-years in the group that received LDA [34]. This finding was in contrast with another retrospective case-control study showing that the thrombosis rate in women with previous antiphospholipid antibody-related recurrent miscarriage is similar to rates in women with idiopathic recurrent miscarriage [35].There are currently no specific treatment recommendations for the prevention of thrombosis in patients with a previous history of antiphospholipid antibody-related pregnancy complications.

Individuals with SLE and antiphospholipid antibodies may develop thrombotic events at a rate of 4% per year and the current EULAR guidelines recommend LDA for primary thrombosis prevention for antiphospholipid antibody-positive patients with SLE[25,36]

2.3 Secondary thromboprophylaxis

Venous thromboembolic events can be separated into provoked or unprovoked events; a provoking factor includes recent hospital admission, or the use of estrogen-containing medication, or pregnancy. In provoked events, even when patients are positive for antiphospholipid antibodies, many physicians administer short courses of anticoagulation (3-6 months) alone and then add thromboprophylaxis at the time of haemostatic stress in the future as one would do in any individual who had a previous thrombotic event. Nevertheless, the presence of high risk aPL profile (e.g., triple positivity for lupus anticoagulant, anti-cardiolipin and anti-β2GPI antibodies) and/or thrombotic events occurring in unusual sites might require secondary thromboprophylaxis for longer than 6 months.

Unprovoked venous events and arterial events are also of great concern. Treatment is mainly based on indefinite anticoagulation with vitamin K antagonists (for example, warfarin) or occasionally, low molecular weight heparin (LMWH)[25]. More recently, the use of direct oral anticoagulants (DOACs) has been investigated for venous events[36].

<u>Vitamin K Antagonists</u>

Two systematic reviews on the use of vitamin K antagonists have been published [4,37]. Lim *et al.* included three RCTs involving patients with APS with a history of arterial and venous thromboembolism[37], and two of the RCTs focused on the intensity of the warfarin that was administered [38,39]. Both showed comparable rates of thrombosis and bleeding in patients treated with vitamin K antagonists targeted to achieve an international normalized ratio (INR, a parameter used to standardize prothrombin time) of 2–3, compared with a target INR of 3–4 (high-intensity). However, the time in time in therapeutic range in the first study for the INR 3-4 arm was only 14%[39]. Based on these data, recommended therapy for

patients with venous and arterial non-cerebral events included indefinite oral anticoagulation with a target INR of 2–3, while for patients who had had a previous stroke it was LDA or vitamin K antagonists with a target INR of 1.4–2.8[40].However, it must be pointed out that both of these trials excluded high-risk patients with recurrent vascular events despite anticoagulation, and according to current guidelines these patients may require high intensity vitamin K antagonists. By contrast, Ruiz-Irastorza *et al.* conducted a systematic review based on twelve cohort studies and four RCTs involving a total of 1,740 patients[4]. Most of the reviewed studies were of evidence level II/III. In general, recurrent thrombotic events in these studies occurred in patients on vitamin K antagonists with an INR <3. Patients who had previous arterial events were at increased risk of recurrence when treated with oral anticoagulation to a target INR of 2-3. Notably, recurrences were infrequent among patients treated with vitamin K antagonists with a target INR of 3-4[4]. In conclusion, the recommendations from this systematic review were to treat patients with a first time venous event and definitive APS with warfarin at a target INR 2-3 and with a target INR >3 in case of recurrent venous events and arterial events[4].

Direct oral anti-coagulants

The use of the novel anti-coagulants would be expected to improve the quality of life of APS patients. These agents, in fact, have fewer drug interactions and dietary restrictions compared with VKA, and more predictable anti-coagulant effects with fixed dosing regiments, making it unnecessary to routinely monitor anti-coagulant intensity. However, the lack of INR monitoring may represent a downfall of novel anti-coagulant therapy, introducing variability in patients' adherence compliance.

Rivaroxaban (a direct anti-X agent) has beenapproved by the European Medicines Agency for the prevention of stroke and systemic embolism in patients with atrial fibrillation, and for venous thromboembolic events management.

Rivaroxaban was compared to warfarin (INR target 2-3) for secondary thromboprophylaxis in APS with previous venous thromboembolism in an open-label, multi-centre RCT including 116 patients (the RAPS trial)[41]. The trial did not reach its primary endpoint defined as the change in endogenous thrombin potential at day 42 (geometric mean 1,086 nmol/L per min, 95% CI 957-1,233 vs 548, 484-621, treatment effect 2·0, 95% CI 1·7-2·4, p<0·0001) (i.e., it did not reach the non-inferiority threshold), although peak thrombin generation was lower in the rivaroxaban group (56 nmol/L, 95% CI 47-66 vs 86 nmol/L, 72-102, treatment effect 0·6, 95% CI 0·5-0·8, p=0·0006) and therefore rivaroxaban may be an alternative to vitamin K antagonist treatment[41]. Furthermore, complement activation products of the classical pathway and terminal pathway, C3a and C5a, and SC5b-9, respectively, were significantly reduced in patients randomized to rivaroxaban, highlighting that rivaroxaban may have other effects besides anticoagulation[42]. Further studies assessing the role of DOACs in thrombotic APS are currently ongoing and results are eagerly [43]. Of concern are a handful of case reports

showing severe adverse events — usually recurrent thrombosis, especially arterial events —in patients with thrombotic APS treated with DOACs[44–46].

The prospective, nested cohort study Antiphospholipid Antibodies and Stroke Study (APASS study) included 1,770 patients with antiphospholipid antibody-related ischaemic stroke and compared the efficacy of LDA (N=889) versus warfarin (N=881) on a composite outcome of death, stroke, TIA, myocardial infarction, DVT, PE, and other systemic thrombotic events [47]. No significant differences in event rate between LDA (RR, 0.94;95th CI, 0.70-1.28; p=071) and warfarin (RR, 0.99; 95th CI0.75-1.31; p=0.94) were observed. However, a major drawback was that patients in the APASS study did not meet the APS classification criteria since antiphospholipid antibodies were only measured once (instead of twice with a 12-week interim)[48]. It is therefore difficult to conclude that the cohort consisted of patients with persistent antiphospholipid antibodies (i.e., fulfilling the APS criteria) [47].

Hydroxychloroquine

The efficacy of hydroxychloroquine in reducing thrombotic rates was first reported in patients with SLE [49]. One paper showed a reduction of thrombotic events in patients who were treated with hydroxychloroquine compared to those who were not with a hazard ratio of 0.28[50]. Schmidt-Tanguy *et al.*[51]showed that in patients with thrombotic APS (N=40), hydroxychloroquine combined with vitamin K antagonists (target INR 2-3) was not associated with recurrent thromboembolic events, whereas 30% in the control group (treated with vitamin K antagonists alone) experienced a recurrent event (p=0.0086). In summary, with the limit of available evidence, a role for hydroxychloroquine in the prevention of thrombosis can be considered.

Catastrophic APS

Lastly, acute management in patients with CAPS is based on anticoagulation, corticosteroids and plasma exchange and/or intravenous immunoglobulin (IVIG) administration according to expert opinions based on data from the CAPS registry[52]. However, no prospective trials have been conducted. Box 2 outlines the current recommendations for the prevention and treatment of patients with antiphospholipid antibodies and APS in the setting of thrombosis[7][4].

Conclusion

Referring to treatments, while current therapeutic options remain confined to long-term anti-coagulation with VKA, the future holds much promise with the identification of novel potential targets, many of which are currently under

investigation.

A real life observational analysis from a multi-centre cohort of 177 patients with thrombotic APS and a median follow up of 5 years (range 1-26) showed that the thrombotic recurrence rate in APS was as high as 7.5 per 100 patient-years in the five years following the first event despite anticoagulation. Diabetes mellitus, inherited thrombophilia and oral anticoagulation discontinuation were independent risk factors for recurrences[53]. As such, many clinical APS experts feel that patients who have previous arterial thrombosis or recurrent thrombotic events whilst being treated with warfarin with an INR 2-3 require a more aggressive approach towards secondary prophylaxis, despite few high-quality studies[4,54]. Options are either high intensity vitamin K antagonist treatment (INR 3-4) or vitamin K antagonists (INR 2-3) combined with other agents such as antiplatelet agents.

The challenge will be to design prospective randomized controlled clinical trials to provide the evidence necessary to support integration of novel therapies into clinical practice. Ideally, the task for the future will be to tailor the APS management, taking into account the antiphospholipid antibody profile and clinical manifestations.

Box 1: Most frequent manifestations of Thrombotic APS [Cervera et al.]

- Most frequent thrombotic manifestations : deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Most frequent arterial manifestations: neurological manifestations (stroke or transient ischemic attacks)
- Other neurological features of APS: migraine headaches, memory loss and epilepsy.
- Most frequent haematological and dermatological manifestations: thrombocytopenia and *livedo reticularis*

Box 2: Management of patients with antiphospholipid antibody-and antiphospholipid syndrome-related thrombosis - adapted from the recommendations of the 13th European Task Force on Antiphospholipid antibodies.

Treatment recommendations adapted from the evidence-based recommendations for the prevention and long-term management of thrombosis in individuals who are positive for antiphospholipid antibodies.

Primary thromboprophylaxis

The general measures for all individuals with a high-risk aPL profile** regardless of thrombosis history, concomitant SLE, or other features of APS are to include maintaining strict control of cardiovascular risk factors.

All individuals with persistent aPL should receive thromboprophylaxis with standard doses of LMWH in high-risk situations (surgery, prolonged immobilization and post-partum).

Long-term primary thromboprophylaxis with LDA is recommended in patients with a high-risk aPL profile*, especially if other thrombotic risk factors or concomitant systemic autoimmune diseases are present. This thrombotic risk needs to be balanced against the known bleeding risks of LDA.

In patients with SLE who have antiphospholipid antibodies background therapy should also included hydroxychloroquine.

Secondary thromboprophylaxis

Treatment groups

- aPL-positive patients with arterial or venous thrombosis not meeting the criteria for APS* should be managed in the same way as aPL-negative patients with similar thrombotic events
- Patients with definite APS and first venous event should receive oral anticoagulant therapy to a target INR of 2.0–3.0

- Patients with definite APS and arterial thrombosis should receive vitamin K antagonists with a target INR >3.0 or vitamin K antagonists with a target INR of 2-3 in combination with an anti-platelet agent (LDA)
- Bleeding risk should always be assessed before commencing high-intensity anticoagulant or combined anti-aggregant and anticoagulant therapy
- For patients without SLE with a first, non-cardioembolic cerebral arterial event who have a low-risk aPL profile*** and reversible trigger factors, antiplatelet agents on an individual basis should be considered

Duration of treatment

- Indefinite duration of therapy in patients with definite APS** and thrombosis
- Anti-coagulation could be limited to 6 months in patients with a first venous event who have a low-risk aPL profile*** and a known transient precipitating factor

Refractory and difficult cases

Possible alternative therapies for patients with recurrent thrombosis, fluctuating INR levels, major bleeding, or who are at high risk for major bleeding, include long-term LMWH, hydroxychloroquine (200-400mg/day) or statins

*High-risk aPL profile: LA positivity, triple positivity (LA + aCL + anti-ßβ2-glycoprotein I antibodies), isolated, persistently positive aCL at medium-high titres; ** Classification criteria for definite APS , ***Low-risk aPL profile: isolated, intermittently positive aCL or anti-ßβ2-glycoprotein I at low-medium titres.

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