Research Article

An Update on Antiphospholipid Syndrome Including C APS & Obstetric Management - A Case Report having Prior 7 Pregnancy Losses Presenting with Stroke following OC Intake - Completely Reversed with LMWH, Methyl Prednisolone &iv IgG's with Update of Recent Literature

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Abstract

Antiphospholipid syndrome (APS) represents an autoimmune thrombo inflammatory condition that can present with different clinical phenotypes. Here we present a report of a case having a history of Recurrent pregnancy losses (RPL) (prior 7 pregnancy losses) in which 1 was at 7mth or 3rd trimester, rest 1st trimester (at 2-3 months) all missed abortions with no live child. Lupus anticoagulant (LA) was positive. After visiting another gynecologist following oral contraception receipt she developed a right-sided stroke involving both the right upper and lower limb along with slurred speech. She reached us 4 months following the stroke onset when her weakness and slurred speech improved completely with low molecular weight heparin (LMWH); iv Methyl prednisolonex3 doses 1g along with wysolone(30mg) subsequently followed by IV immunoglobulins. Here we have further provided an update on the latest advances in APS research and how this patient was approached and how a future obstetrical approach is warranted although she falls in the worst category of APS as detailed in an update of literature and this case report in view of the history of APS with the thrombotic event along with positive TPO antibodies.

Keywords: *APS; LA positive; Stroke; LMWH; Methylprednisolone; RPL.*

1.Introduction

Earlier we have reviewed the management of recurrent pregnancy loss(RPL), various etiologies including various Antiphospholipid antibodies along with the role of antithyroid antibodies in RPL[1-4]. Antiphospholipid syndrome (APS) represents an autoimmune thrombo inflammatory condition that can cause harm as well as disastrous actions on patients along with their families. APS might implicate any kind of circulatory bed within the body. Whereas the deep veins of the lower limbs along with the arterial circulation of the brain are the commonest areas for thrombosis, any tissue or organ might get implicated [5,6]. Obstetrical complications are further well acknowledged in APS, which includes eclampsia or robust pre-eclampsia which leads to preterm birth along with fetal death following the 10th week of pregnancy [5,7]. Other than thrombosis as well as pregnancy, the rest of the complications might include consistent thrombocytopaenia, hemolytic anemia, livedo reticularis, APS nephropathy as well as cognitive impairment have been correlated with APS as well as usually labeled as "non criteria" or "extra criteria" presentations[8]. APS can be classified as primary APS which takes place alone or

secondary APS that occurs in correlation with other autoimmune syndromes, the commonest one being SLE. Catastrophic Antiphospholipid syndrome(CAPS), which has the properties of thrombi in a lot of small vascular beds, resulting in multi-organ failure along with great mortality rates, gets generated in a small subgroup of APS patients[9].The calculated population prevalence of APS is 50 cases /100,00,with an annual incidence of 2.1/100,00,[10].Studies that are just observational without proper follow up, have demonstrated that Antiphospholipid antibodies (aPL)might be positive in upto 13% of patients with stroke, 11% with myocardial infarction(MI) as well as 9.5% of patients with deep vein thrombosis(DVT)[11]. The exact prevalence of aPL in healthy population has yet to be evaluated.

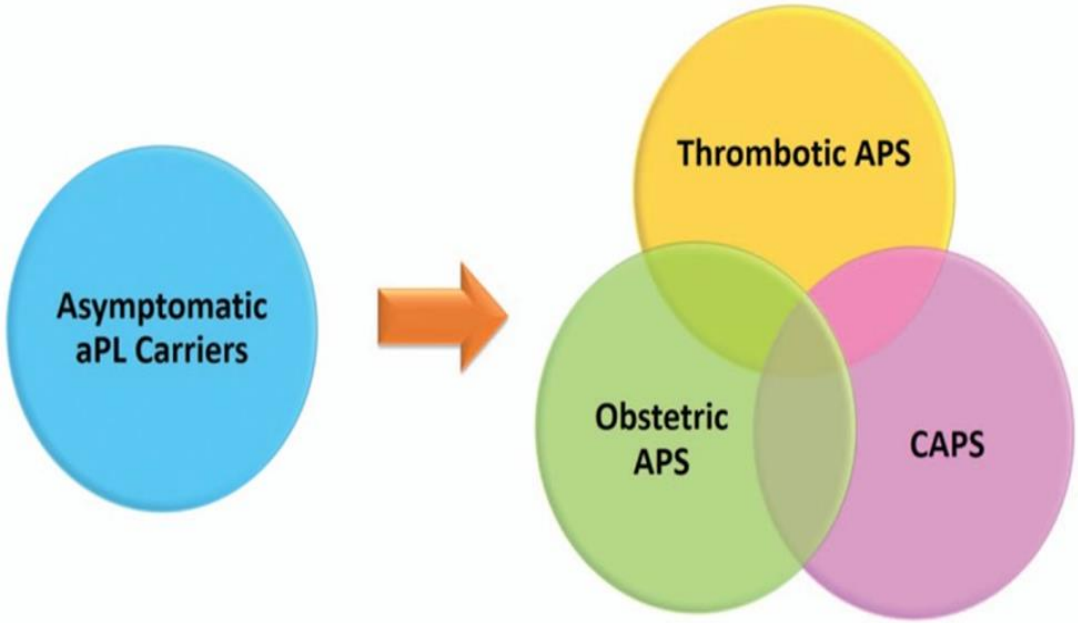

Figure 1: Courtesy ref no-13-Overlapping clinical spectrum of antiphospholipid syndrome (APS). aPL: Antiphospholipid antibodies; CAPS: Catastrophic antiphospholipid syndrome.

For the classification of APS,a minimum of 1 or greater classical aPL(anticardiolipin)(aCL)IgG or IgM,anti β2-glycoprotein -1(aβ1GPI) IgG or IgM along with Lupus Anticoagulant(LA) in relevance of a thrombotic process or some kinds of pregnancy morbidity[12]. Nevertheless in everyday clinical scenario, APS might be much more complicated as well as represents a disease spectrum (figure1) (Rev in ref 13]. Whereas there are certain APS cases with apparently isolated thrombotic or obstetrical complications,there are further patients who persistently possess posiive aPL patients that are persisting as well as only 'non-criteria' presentation. Further there are a group comprising of lesser patients who generate CAPS. Here the present literature in context of APS clinical care with certain updates in association with

2.Pathophysiology Updates

Antiphospholipid antibodies (aPL) represent a heterogenous type of auto antibodies which have a significant part in the etiopathogenesis of APS through their crosstalk with plasma proteins like β2-glycoprotein -1(β1GPI),prothrombin, thrombomodulin, plasminogen, antithrombin III, protein C, protein S, annexin II, as well as annexin V[14-16].Crucial aPL modulated prothrombotic modes implicate the stimulation of endothelial cells [17], monocytes[18], platelets[19], coagulation factors as well as a complement proteins [20]. Moreover aPL have an impact on the fibrinolytic along with coagulation pathways, besides stimulation of placental inflammation as well as damage [21].Basically APS was [reviewed extensively in ref 22, 23],thus here only salient points with regards to certain recent work that gives more insight to us in taking our knowledge of APS pathogenesis at much deeper level.

Micro RNAs (mi RNAs) represent single stranded small non coding RNAs which have a significant part in cellular crosstalk. They act to control the expression of messenger RNAs that possess complementary sequences to mi RNAs. Various researchers have evaluated the properties of mi RNAs recently with regards to the pathogenesis of APS[24-27].An intriguing study observed that forcing the over expression of some mi RNAs(miR 19b as well as miR20a)in cell lines that express tissue factors diminished amounts of tissue factors messenger RNAs,in addition to cellular procoagulant action [25].It seems that monocytes belonging to APS patients possess markedly lesser amounts of miR 19b as well as miR20a in cell lines that express tissue factors in contrast to healthy donor neutrophils, monocytes as well as endothelial cells with purified aPL IgG diminished the expression of different mi RNAs[27].Simultaneously, differential expression of circulating mi RNAs can discriminate APS patients from healthy controls [26];like transcriptomic evaluation of plasmacytoid dendritic cells from APS as well as without systemic lupus erythematosus (SLE) patients, pointing that lesser amounts of mi RNA expression(miR 361-5p, miR 128-3p, miR181a-2-3p as well as other correlates with an escalated type1 interferon signature[24].More studies are required for further knowledge regarding part of mi RNAs in APS disease manipulation, along with the degree to which mi RNAs might play as treatment targets.

A lot of studies from the general thrombosis publications have demonstrated that activated neutrophils, as well as specifically neutrophils extracellular traps(NET) generation, aid in the progression of thrombi influencing the arterial, venous along with microscopic vascular beds[28].Further NETs have been felt to be responsible for the pathogenesis of APS.During 2015 Zuo 's group documented that sera from APS patients along with purified aPL, stimulate neutrophils to liberate NETs[13,29].The potential in vivo context of this finding has got validated in mouse models of aPL-modulated large vein thrombosis,where both removal of neutrophils or the digestion of NETs acts as protective[30].Further neutrophils from APS patients seem to possess enhanced adhesive properties that is based on the activated type of integrin Mac 1.This proadhesive characteristic exaggerates neutrophil- endothelial cross talk, accelerates NET

generation, besides potentiating lessening the threshold for thrombosis[31].

Sera belonging to primary APS patients possess escalated type1 interferon action [32],that has got corroborated by a lot of groups[33].Intriguingly transcriptomic evaluation of neutrophils from APS patients documented an exaggerated expression of genes in the context of besides interferon signaling, cellular defense as well as cell-cell adhesion.A specific gene that encodes P-Selectin glycoprotein ligand 1(PSGL-1) was robustly upregulated as well as potentially implicated in thrombus generation.Actually, an in vivo model illustrated that deficit of PSGL-1 conferred protection on mice from aPL- escalated thrombus generation[34]. The context of this pathway in patients has to be evaluated fully.

Treatments which target NET generation possess the capacity of treating thrombotic diseases [28].Like selective agonism of adenosine A2A receptor represses aPL-modulated neutrophils NETosis in a protein kinase A(PKA) –based manner[35]. A2A agonism further decreases thrombosis in Inferior vena cava(IVC) of both control mice along with mice receiving aPL.Dipyridamole, that is accepted to escalate adenosine signaling by escalation of extracellular amounts of adenosine besides impacting the degradation of cAMP, further represses aPL-modulated NETosis along with amelioration of venous thrombosis in mice. Intriguingly CD39 as well as CD 73, that results in generation of AMP from extracellular ATP initially as well as then adenosine confers protection to experimental animals from aPL-stimulated fetal loss[36]. Summarizing, it is feasible that heterogenous modes are participating in the pro thrombotic along with pro inflammatory modes modulated by aPL. A lot of significance is being attributed to mi RNAs in APS pathogenesis. Neutrophils along with NET generation have been evaluated only recently, with future work is required for getting insight regarding the degree to which neutrophils represent viable drug targets in cases with APS along with how neutrophils crosstalk with other known actors in APS pathophysiology like endothelial cells as well as platelets. It is posited that treatments which target NETs might be a luring strategy, atleast for a subset of cases of APS.

3.0 Primary prophylaxis for thrombosis

One most difficult problem faced in APS management is the treatment approach for asymptomatic aPL positive subjects. We have had the knowledge that constantly positive aPL are correlated with an escalated chance of arterial as well as venous thrombosis[37]. Nevertheless, precise quantification of this risk has proved to be tough in view of inconsistely applied aPL laboratory criteria besides the multiple factors implicated in thrombosis risk, along with a lot of confounding factors like underlying autoimmune diseases along with action of medicines [37]. As a routine Primary prophylaxis for thrombosis is tough in asymptomatic aPL carriers continues to be controversial in view of minimal as well as data of very low quality [38]. Present proof as well as recommendations for Primary prophylaxis for thrombosisin context to APS is summarized.

3.1 aPL possessing clinical significance

The initial step in risk stratification in an aPL positive subject is to find if a positive aPL if a positive aPL possesses a clinically significant role [39]. Transiently positive aPL are common specifically at the time of concomitant infections, as well as usually not correlated with thrombosis. In a recent systematic review of the 297 infection - correlated aPL positive patients(24.6% totally agreed with the Sydney classification criteria) demonstrated that 75.4% of positive aPL found at the time of infection are momentary [39].In a prospective cohort study where blood samples from healthy donors demonstrated 10%baseline that were positive for aCL or LA, nevertheless, 12 mths following that only 1% of these blood samples continued to be positive for aCL or LA[40].Decision of if positive aPL possesses a clinically significant role needs to utilize the 2006 revised APS classification criteria[12].Initially, a positive aPL requires to be at moderate/high titre that can get defined as more than 99th percentile cutoff obtained from blood samples derived from healthy controls.2) A positive aPL needs to be constantly existing for a minimum of 12 wks. Lupus Anticoagulant evaluation needs to be dependent on the International Society of Thrombosis and Haemostasis (ISTH) recommendations[41].Whereas ''criteria aPL"(IgG/ IgM of aCL, IgG/ IgM of aβ1GPI, as well as LA) are the commonly examined as well as easily assessable in all types of clinical settings [42], there exist a lot of non 'criteria aPL"(like antiphosphatidyl serine /prothrombin (anti-PS/PT, anti domain I aβ1GPI,IgA isotypes of aCL as well as aβ1GPI, as well as APHL) that got invented in the last 20yrs as well as do not belong to the revised APS classification criteria[43].Right now they are utilized in research settings, not being accessible by most clinicians. A document from the 15TH International Congress on Antiphospholipid antibodies Task Force gave a summary of different non criteria aPL [43].Whereas some of the these antibodies did display attractive clinical usefulness in isolation of APS subjects[43],greater data are required prior to recommending them for routine evaluation, As per Zhou et al.[13] A lot of these tests(like high titer of anti-PS/PT,anti domain I aβ1GPI have the capacity to drive APS pathogenesis as well as future multicenter studies need to analyze their significance.

3.2 Incidence of Thrombosis in aPL positive carriers

A lot of factors can initiate thrombosis. Thus the absolute incidence in asymptomatic aPL positive carriers is tough to evaluate, in view of it getting impacted by lot of confounding factors,known(like age, underlying systemic autoimmune disease, CVS risk factors, usual venous thrombosis risks, medicines) along with not known [44].Studies that are currently available possess limitations of small sizes along with study design which usually do not take into account controlling for these different confounding factors. Like, in a prospective study that incorporated 178 asymptomatic aPL positive carriers without receiving any primary prophylaxis, no thrombotic processes were seen in the 36 mths of prospective follow up [45].One more prospective study enrolling 258 asymptomatic subjects having validated persistent aPL positive(of which 54.3% were receiving primary prophylaxis) demonstrated a thrombotic

incidence rate of 1.86%[46].Another prospective observational study carried out by Pengo etal.[47] included 179 asymptomatic isolated persistent LA carriers(of which 23% were receiving primary prophylaxis)with a follow up of 552 patient years. Of these 66% of the subjects were not observed to be carrying any systemic autoimmune diseases. The yearly incidence rate of thrombosis was 1.3%. One more prospective observational study involving 104 aPL carriers that were triple positive (of which 63. 5 % were receiving primary prophylaxis along with 47% having underlying systemic autoimmune disease) with a mean follow up of 4.5yrs demonstrated a thrombosis incidence rate of 5.3%.Out of these studies, neither had a design to control for the primary prophylaxis use, Thus summarizing, thrombosis gets initiated by A lot of factors along with absolute thrombosis index in asymptomatic aPL positive carriers is tough to evaluate. Nevertheless, saying that, triple positive aPL carriers might possess a greater yearly incidence of thrombosis risk. Certain experts in this field have pointed that the yearly incidence in aPL carriers without having any other thrombosis risk is under 1% [44].

3.2a Aspirin

The part of Aspirin in the form of a primary prophylaxis drug in patients with persistently positive aPL continues to be controversial[38].The lone randomized controlled trial (RCT) analyzing the efficacy of aspirin (n=48)vis a vis placebo(n=50) at avoidance of 1st thrombotic process in asymptomatic aPL positive carriers. Their conclusions reached were that daily low dose aspirin(LDA)(81mg) is not better in contrast to placebo in avoidance of thrombotic process(hazard ratio[HR]=1.04.95% Confidence interval[CI]:0.69-1.56[48],although with a lesser event rate being the biggest drawback of this trial. Hence, a lot of experts point that it is underpowered to find any influence of LDA. Results from observational studies actually point towards conferring protection action of aspirin[49-51].An observation of 103 aPL carriers having an average follow up of 64mths validated the utilization of LDA in the form of primary prophylaxis for thrombosis, specifically in the ones with SLE or thrombocytopaenia [51].A Cochrane systematic review conducted recently evaluated the actions of anti platelets or anticoagulant drugs in contrast to placebo for avoidance of thrombotic process in aPL positive subjects. It consisted of 9 studies with a total of 1044 participants, arriving at the conclusions that enough proof to validate the use of aspirin for primary thrombosis avoidance among aPL positive carriers[52]. The 15TH International Congress on Antiphospholipid antibodies acknowledged that we do not possess convincing proof to validate the utilization of aspirin for primary thrombosis avoidance among all persistent aPL positive subjects; nevertheless, a subgroup of patients having simultaneous cardiovascular disease (CVD)risks might get advantage from LDA to avoid 1st thrombosis event[38].The EULAR APS treatment recommendations actually agree with the utilization of aspirin for primary prophylaxis against in thrombosis in patients possessing a high risk aPL profile (like persistent positive LA,double as well as triple positive aPL).

One should not forget however that LDA utilization can be correlated with escalated risk of bleeding. Results from the CVD avoidance studies(although with significantly elder participants in contrast to a lot of aPL/APS patients)has pointed that chronic LDA use is correlated with escalated risk of heavy) Gastrointestinal Tract(GIT) bleeding (OR =1.58, 95% Confidence interval [CI]:1.29-1.95) along with haemorrhagic stroke(OR =1.27, 95% Confidence interval [CI]:1.96-1.68)[53].One more recent population dependent study with 10yrs observation involving 3166 patients receiving LDA(75mg/day)[54],points that the average yearly risk of bleeding in patients on aspirin is 3.36%.The yrly bleeding risk escalates with age, reaching 4.1% at the age 85 or elder[54].The requirement for the avoidance of thrombosis requires to be balanced with the risk of bleeding on thinking of use of LDA in the form of a primary thrombosis prophylaxis drug.

Thus summarizing convincing proof to corroborate the utilization of aspirin for primary prophylaxis against of thrombosis remains absent, specifically for patients without other systemic autoimmune diseases. Persistent aPL positive carriers having simultaneous cardiovascular disease (CVD) risks, high risk profiles or SLE might gain advantage from aspirin for lessening the risks of 1st thrombosis. The risk of bleeding from aspirin needs to be taken into account when deciding regards to primary thrombosis prophylaxis.

3.2b Hydroxychloroquine

Hydroxychloroquine(HCQ) represent a significant disease modulating drug for therapy of systemic autoimmune diseases, specifically for SLE. In case of animal models of therapy of APS with HCQ results in smaller thrombi along with lower persistence for a long enough time[55].Further HCQ might also modulate a decrease in aPL-β1GPI complex binding to the phospholipid bilayers along with human monocytes[56]. Annexin A5 represents an anticoagulant protein which coats the phospholipid bilayers awa thus confers protection from key coagulation enzymatic reactions. An in vitro study illustrated that HCQ therapy can mitigate aPL modulated breakdown of annexin A5 protective cover as well as thus preserve its anticoagulant characteristics [57]. An Intriguing human study documented that greater type1 interferon signature was seen in monocytes from human patients who were not receiving utilization of in contrast to the APS patients receiving it[35]. A prospective follow up involving 144 SLE patients possessing aPL along with144 sex as well as age matched SLE patients not possessing aPL illustrated that utilization of HCQ confers protection against thrombosis in SLE patients with as well as without aPL[50].To our misfortune, an international prospective RCT involving HCQ for primary thrombosis avoidance in persistently positive aPL carriers (without SLE) got terminated recently in view of low enrollment rate along with high cost factor [58]. Nevertheless, prior to cancellation a total number of 20 patients possessing persistently positive aPL without a prior history of thrombosis got recruited.9 patients were randomized to get HCQ as well as 11 did not get it. None of the patients in each group

generated thrombosis in the 1.7 years follow up [62]. Chronic utilization of HCQ(greater than 5yrs) at higher doses(greater than6.5mg/kg /day or greater than1000g cumulative dose) has a correlation with an escalated risk(1%) of retinal toxicity[59].Hence in routine ophthalmological supervision is required in cases who need long term HCQ.

Summarizing studies on mode of action do point that HCQ confers protection against thrombosis potentially. HCQ decreases thrombosis risk in positive aPL SLE patients. No finished studies have as yet analysed its part in primary aPL carriers. HCQ needs to be thought of in aPL carriers possessing underlying systemic autoimmune diseases.

3.2c Statins

Statins that work as 3 –hydroxy-3methyl-glutaryl coenzyme A(HMG-CoA)reductase inhibitors are being utilized for primary as well as secondary CVD avoidance in view of their actions of diminishing cholesterol, anti-inflammatory along with inhibition of thrombosis[60].Fluvastatin receiving mice display thrombi that are smaller significantly, diminished inflammatory molecules (intercellular cell adhesion molecule[ICAM]-1 as well as decreased leukocyte adhesion to endothelial cells in contrast to controls[61]. Monocytes, obtained from 42 thrombotic APS patients that received Fluvastatin for a mth displayed inhibition of tissue factor expression in monocytes [62]. A prospective study comprising of 41 aPL positive subjects who received daily 40mg of Fluvastatin for 3 mths illustrated significantly, diminished circulating proinflammatory as well as prothrombotic biomarkers following therapy[63].At present, no randomized clinical trial of Statins for primary thrombosis avoidance in aPL positive carriers. Summarizing animal as well as human studies on mode of action point that Statins-stimulated alternative actions on target cells might be a promising approach for primary thrombosis prophylaxis awa requires further clinical analysis. aPL carriers with simultaneous CVD risk factors might be the ones suitable for statin medicines.

3.3 Secondary prophylaxis for thrombosis

This terminology is used with regards to the therapy of APS patients following any arterial as well as /or venous thrombotic processes that has been without any provocation. Non provoked thrombotic processes by definition are clotting processes which are without dependence of any main temporary chances for thrombosis like the utilization of oral contraceptives(OC),continuous immobilization or cancer [6,64].The presently mainly utilized therapy for Secondary prophylaxis for thrombosis represent life through anticoagulation with a Vitamin K antagonist, or rarely low molecular weight heparin(LMWH) for patients having contraindication to or do not tolerate Vitamin K antagonist. Recently, direct oral anti coagulants (DOAC)have been analyzed for alternation for Secondary prophylaxis for thrombosis in APS patients.

3.3a Vitamin K antagonists

These Vitamin K antagonists like warfarin have been the primary therapy for thrombotic APS right from historic times. Their effectiveness in avoidance of recurrent thrombosis has got validated in a lot of studies. A Systematic review has pointed that anti coagulation with warfarin of moderate intensity(INR among 2.0 as well as 3.0)decreased the risk of recurrent venous thrombosis by 80-90%[65].A lot of debate has been done regarding the intensity of Vitamin K antagonists treatment in APS patients. Various early observation studies pointed that the ideal anti coagulation methods were the ones that could sustain an INR among 3 as well as 4[66]. Nevertheless, 2 randomized controlled trial (RCT), I in 2000's gave an opposite opinion. A randomized double blind, trial involving 114 APS patients where subjects got randomized to get an INR of 2.0 to 3.0 (i.e moderate intensity) or 3.1 to 4.0(high intensity) [66], demonstrated that high intensity Vitamin K antagonists were not better in contrast to moderate intensity for Secondary prophylaxis for thrombosis [67].Another trial incorporating 109 individuals validated that high intensity Vitamin K antagonists was not better in contrast to the Standardized therapy in avoiding recurrent thrombosis in patients with APS along with correlated with an escalated rate of haemmorhagic complications[68].Depending on the proof of these 2 trials, the present Standard for early management of the thrombotic Antiphospholipid syndrome is moderate intensity Vitamin K antagonists. Those who are cynical with regards to these 2 trials comment that the percentage of participants persistently attained the greater INR target was low as well as occasional APS patients presenting with arterial thrombosis had got recruited. A lot of experts in this topic continue to favour high intensity Vitamin K antagonists of the APS patients presenting with recurrent thrombosis depending on certain unscientific data, besides their personal experience. Despite limited proof, current EULAR APS management guidelines thinks about high intensity Vitamin K antagonists as alternative drug for LMWH for APS patients presenting with recurrent thrombosis[69].In a lot of centres, LDA in combination with a Vitamin K antagonist for Secondary prophylaxis in patients with arterial thromboembolic processes as well as a recent retrospective observation does endorse combination treatment[70].

3.3b Oral Anti coagulants that act Directly

The directly thrombin or factor Xa inhitors like rivaroxaban or apixabam have been in limelight recently for thrombosis avoidance in case of patients presenting with Atrial Fibrillation along with the ones getting hip or knee replacement, besides for therapy of Deep Venous Thrombosis [71]. Evaluation retrospectively of DOAC's documented utilization of DOAC's for Secondary prophylaxis for thrombosis in APS patients contradictory data as far as effectiveness is concerned[72].Three RCT's till now have analysed the efficacy of DOAC's for Secondary prophylaxis for thrombosis in APS patients. Of these the 1st study represented an open label RC noninferiority study involving 166(of which 28%that were triple positive) APS patients that compared rivaroxaban in contrast to warfarin. The primary outcome was not

clinical but instead the degree of alteration in endogenous thrombin potential (ETP)from randomization till day 42, with noninferiority kept at lower than 20%variation from the warfarin therapy arm[73].The outcome of this study did not meet its primary endpoint, that had been kept at noninferiority threshold. Significantly, no thrombosis or heavy bleeding was encountered in any group. A 2ND randomized an open label study analysed the efficacy of rivaroxaban in contrast to warfarin in case of 120 high risk(that were triple positive by definition)that had an average follow up of 569 days[74].In this case the primary outcome was accumulated thrombotic processes, heavy bleeding, along with vascular demise that were documented to be Significantly greater in the rivaroxaban group in contrast to warfarin(HR-7.4,95%CI1.7-32.9,P=0.008)at the time of interim Evaluation. Seven arterial thrombosis as well as 1 venous thrombosis was revealed in the rivaroxaban group, while none in warfarin group. In view of escalated risk as well as no visible advantages of rivaroxaban in high risk APS patients, this study was closed early [74]. The maximum recent trial, which was a randomized noninferiority study that was reported in October 19, did not illustrate noninferiority of rivaroxaban in contrast to warfarin in the form of Secondary prophylaxis for thrombosis in APS patients[75]. A little escalated risk of arterial thrombosis was also seen (RR19,95%CI-1,1-321.9) [75].A further ongoing RCT (ASTRO-APS) that is analyzing DOAC's utilization of as well as no obvious advantages Secondary prophylaxis for thrombosis in APS patients[72]. Summarizing right now no data to validate the utilization of DOAC's for thrombotic processes. Moreover, there is proof against the utilization of DOAC's for Secondary prophylaxis for thrombosis in high risk APS patients as well as specifically with a history of an arterial presentation (i.e not astonishing since DOAC's have not got approved for arterial indications in the general population).It is not apparent why DOAC's were a failure. Dosage that was suboptimal along with Standardised anticoagulation intensity(neither trial Standardised the anticoagulation intensity with anti Xa factor activity) could be aiding factors. Probably these drugs might in the end have a part in a subgroup of APS patients, but more evaluation is definitely required prior to that. Thus moderate intensity warfarin at present is the primary approach for Secondary prophylaxis for thrombosis in APS patients. LDA can further be added in patients presenting with arterial thrombosis. For that subgroup of cases who generate thrombosis when still receiving warfarin, alternative treatment with LMWH or high intensity warfarin can be thought of. At present none randomized controlled results endorse the utilization of DOAC's in case of thrombotic APS patients, as well as DOAC's need to be not utilized in case of APS patients that are high risk unless the practitioner is under particular situations.

4.Management of APS patients in relation to Obstetrics

The Management of patients with aPL or APS are mostly dependent on small trials, along with expert opinions. Present recommended therapy approaches as well as proof present

4.1 Asymptomatic aPL carriers

Contradictory results are the with regards to the best option for Management of the patients possessing persistently escalated aPL titers who have never witnessed any pregnancy complications or thrombosis 2RCT as well as 1 retrospective observation of pregnant ladies having positive aPL, however no SLE did not document any variation in live birth rate (LBR) with the utilization of LDA(75mg-81mg/day by definition)[76].A RCT comprising of lot of high risk pregnancy population (n=1176),that included patients with high mothers age, hypertension, diabetes mellitus(DM),low amount pregnancy associated protein A along with positive aPL documented that LDA led to a significantly lesser incidence of preterm preeclampsia [77].Present expert agreement advocates close fetal as well as maternal watch along with thinking of LDA in asymptomatic aPL carriers as well as high risk profiles like triple positive or persistently escalated aPL positive LA[6,69].

4.2a PL carriers Presenting only with recurrent 1st trimester pregnancy loss (no thrombosis treatment)

Contradictory results are again documented with regards to the best option for management of the patients. Three RCT's pointing to a significantly greater LBR with combining LDH along with either LMWH or heparin [78].Two RCT's further did not find any variation in LBR among LDH by itself as well as LDH along with heparin combinations[79].One meta-analysis of all finished trials has a slight preference for the utilization of LDH along with LMWH or heparin combinations[11].Present recommendations advocate adding LMWH or heparin prophylaxis to LDA during pregnancy for the ladies presenting only with recurrent 1st trimester pregnancy loss[69].

4.3a PL carriers Presenting with previous history of preeclampsia as well as/or2ndor3rd trimester pregnancy loss (no thrombosis history)

A RCT which analyzed 110 positive aPL ladies with previous history of preeclampsia/APH or late term pregnancy loss pointed to utilization of LDH along with LMWH, that got correlated with significantly lesser incidence of severe preeclampsia, placental rupture as well as low birth weight [80].Hence recommendations advocate utilization of LDH along with LMWH or heparin for this particular group of ladies in pregnancy[6,69].

4.4a PL positive ladies with history of previous thrombosis

A small observational study comprising of 20 pregnant ladies with thrombotic APS who got 100mg aspirin/day as well as therapeutic LMWH, illustrated a LBR of 91.3% [81]. Nevertheless, an escalated incidence of Obstetrics complications (preeclampsia-32.8% as well as preterm delivery-42.9%) persistently was seen. We have in our knowledge that thromboembolic processes in APS patients are significantly correlated with an escalated future thrombosis risk as well as Obstetrics complications.

The Obstetrics Management agreement for aPL positive ladies history of previous thromboembolic processes is utilization of LDH along with therapeutic LMWH during pregnancy [44,69].

4.5 Post Partum Management Of aPL positive ladies

In general population aw, women in the post partum period present a greater high risk of history of thrombosis[82].Thus recommendations advocate in aPL positive ladies who never gave history of thrombosis utilization of prophylactic LMWH 6wks as well as women with APS having history of thrombosis restart therapeutic anticoagulants(LMWH or warfarin)immediately to avoid post partum thrombosis[6,44] Summarizing Obstetrics APS Management is complicated as well as present recommendations are usually dependent on low quality results as well as expert agreement. Education of patients as well as counseling with regards to the Obstetrics risks is significant. Tailoring of therapy that is individualized as per the patients aPL profile along with Obstetrics as well as thrombosis history.

5.Capacity of newer therapy /pathways needing attention

APS constitutes a complicated disease in which multiple systems get implicated. The current pathophysiology studies have involved a lot of non thrombotic pathways that aid in different APS clinical presentations. In a lot of cases classical anti coagulation is usually ineffiacious for non criteria APS clinical presentations,that might have their initiation in the microvascular. In this we provide a summary with regards to the present proof with regards to therapy of APS with medicines that are different from anti coagulants, as well as certain emerging newer pharmacological drugs needing attention.

5.1 Rituximab

B cells have a significant part in the APS etiopathogenesis. Studies conducted in vivo have illustrated that inhibition of B cells avoids disease initiation as well as escalates the survival in APS murine models [83]. Various case reports have documented the success in utilization of Rituximab in APS patients presenting with robust thrombocytopaenia, haemolytic anaemia, skin ulcers or necrosis, aPL nephropathy along with catastrophic APS[84]. RITAPS Trial was a pilot open label phase II study whose objective was to analyse the safety of Rituximab in adult primary APS patients[85].These observations point that Rituximab is safe in APS patients as well as might be efficacious in regulating for non-criteria APS clinical presentations like thrombocytopaenia, skin ulcers as well as APS nephropathy[85].

5.2 Eculizumab

A lot of significance has been attributed to the complement getting activated in the etiopathogenesis of APS. Like murine studies illustrated that activation of complement is needed for the aPL modulated pregnancy loss[86]. Inhibituion of complement avoids fetal growth retardation as well as can further decrease aPL modulated generation of thrombosis[83,86]. Eculizumab represents a humanized

monoclonal antibody that has presently got approval for atypical haemolytic uraemic syndrome as well as paroxysmal nocturnal haematuria [87]. This antibody binds to C5 as well as avoids the cleavage of C5a to C5b[87].A lot of case series have pointed its effectiveness in the therapy of recalcitrant APS,CAPS, as well as SLE thrombotic microangiopathy [83,87]. An ongoing clinical trial with the objective of analysing the safety as well as tolerability of Eculizumab in APS renal transplant patients along with analysing its effectiveness on thrombosis avoidance (Clinical Trials. gov Identifier: NCT 01029587).

5.3 Adenosine receptor Agonists along with Defibrotide

Defibrotide represents a mixture of oligonucleotides obtained from the regulated depolymerization of porcine intestinal mucosal DNA with anti thrombotic, antiischaemic as well as anti inflammatory actions. It binds to the Vascular endothelium, manipulates platelets actions, facilitates fibrinolysis, reduces thrombin formation along with action as well as decrease circulating action of plasminogen activator inhibitor type 1(PAI-1)[88,89].It might further work in the form of an Adenosine receptor Agonist as well as is believed to have specific affinity for receptors A1 as well as A2[90].

A lot of studies have pointed to the capacity of Defibrotide in different Vascular conditions, that includes peripheral Vascular disease, microvascular thrombotic states as well as chemotherapy associated haemolytic uraemic syndrome [91].Initially Defibrotide received approval for the therapy of thrombophlebitis as well as prophylaxis for DVT in Italy [91,92].Further it received approval in USA as well as Europe for therapy of robust hepatic venoocclusive disease (sVOD) subsequent to high dose chemotherapy as well as autologous bone marrow transplantation. Knowing the functions in the form of endothelium-protective substance as well as Adenosine receptor Agonist Defibrotide got utilized with success for treating recalcitrant CAPS patient[93]. Defibrotide seems to possess acceptable tolerance with absence of systemic anticoagulant action, that could point to a probable treatment benefit over rest of the treatments available [94].Further research is required for evaluating effectiveness as well as safety of Defibrotide in APS, particularly in treatment -recalcitrant microvascular disease as well as CAPS.

5.4 Rest of Strategies

Coenzyme Q10(CoQ10) seems to possess a significant role in the electron transport chain of the mitochondrial membrane with enough CoQ10) amount confers protection to cells from proteinoxidation. Administration of CoQ10 has been evaluated in trials for coronary artery disease, where it reduced the generation of proinflammatory cytokines [95].A recent RCT analysed the action of ubiquinol (that is a CoQ10 supplement)on prothrombotic as well as proinflammatory mediators in APS patients[96].This study observed that ubiquinol enhanced endothelial function as well as reduced monocytes expression of prothrombotic mediators in APS patients[96].They pointed to ubiquinol might further enhance the present Standardised APS therapies[96] In the 2019 International Congress on Antiphospholipid

antibodies-other potential therapeutic targets for APS like agents targeting plasma cells as well as interferons, got detailed.(http://icapaconference.com).If neutralization of antibody –generating plasma cells or interferons might ameliorate the noncriteria manifestations.

6.Conclusions

Substances that target B Cells as well as complement activation have got utilized for the noncriteria manifestations management like thrombocytopaenia nephropathy, thrombotic microangiopathy. greater results are required prior to any of these substances get formal recommendation. Current insights in APS etiopathogenesis, specifically part of NETosis in APS might give pathways for targeted therapies that might alter the escalatingly personalized management of APS. Thus APS represents a complicated thrombo inflammatory syndrome with different manifestations. Primary thrombosis prophylaxis needs to take an individualized stratification strategy for making a personalized utilization of LDA, HCQ, as well as or statins. Moderate intensity warfarin continues to be the primary approach for secondary thrombosis prophylaxis in APS patients. DOAC's need to be prevented in triple positive APS patients, part with history of arterial manifestations. Obstetrical Management of APS needs to be tailored on the subjects profile, as well as obstetrical along with thrombosis history. Pharmacological substances beyond anticoagulants can be thought of for management of non-criteria manifestations, despite need for greater data.

Case Report

A 30YR old patient with history of previous 7 missed abortions/intrauterine fetal death (IUFD) presented to our centre on 20/3/21with history of weakness in right upper and lower limb with slurring of speech,was examined by a neurologist who put her on 150mg low dose aspirin ,after CT normal-Patient came to us after that on 20/3/2021 with no relief initially for relief of stroke and then subsequently for conception for future live baby.

M/F 7yrs. Cycles were regular 3-5/30 days regular Wt -70kg ,Ht-168cn,BP 125/87mmHg,BMI-24.81 Kg/m^2, Her abortions were 1^{st} preterm delivery at 7 mth with IUFD sudden pain abdomen, dead fetus removed by ?pge2 ,iv oxytocin ,expulsion then 2^{nd} -21/2 mth –no D&C,3^{RD} -3mth –missed Abortion, D&C done in jammu,4^{th} 2mth ,no D &C Rest 3 mth missed D&C done. Patient had gone to a centre in Ludhiana where she was put on Oral Contraceptives(OC's) (Indication ?). Now she had presented with sudden weakness in right upper and lower limb since 21^{st} December 2020. On neurology consulation by a neurologist that time –CT Scan Head was told normal verbally and ecosprin 150 mg was added. With no relief she came to us with positive Lupus A nticoagulant and rest of APL profile negative Reports for APL Profile early in Jan 2021

PTT and mixing studies, PLASMA		
PTT(Test)	97.4	**high** 31.9-42.7 sec
PTTControl(normalpooled plasma)	32.2	31.9-42.7 sec
PTT(Test+Control) 1:1	49.9 sec	
DRV SCREEN TIME ,PLASMA		
DRVV SCREEN (TEST)	115.80	**High32**. 82-48.90sec
Method ;clot based automated coagulometer		
DRVV SCREEN CONTROL	38.20	32.82-48.90 1.46
DRVV SCREEN RATIO	3.03	**High** 0.82-1.22 ratio
DRVV CONFIRM PLASMA		
DRVV CONFIRMATORY (TEST)	45.3	**High** 27,.59-34.55sec
DEVV CONFIRMATORY(CONTROL)	31.1	27.59-34.55sec
DRVV CONFIRM RATIO	1.46	**High** 0.93-1.17
Normalized Ratio(DRVV SCREEN RATIO/	2.08	**High** 0.82-1.14
DRVV CONFIRM RATIO		
Lupus Anticoagulant	**present**	absent
ABS to Extractable Nuclear Antigen		
(ANA BLOT),Serum		
Rheumatology Profile-2 ,Serum		
Smith Antibodies	negative(0)	
U1SM/RNP Antibodies	negative (0)	
SS-A Antibodies	negative(0)	
RO0-52 Antibodies	negative(0)	
SS –B Antibodies	negative(0)	
Anti Histone Antibodies,Serum		
Anti Histone Antibodies	negative (0)	
Anti Centromere Antibodies,Serum		
Anti Centromere Ab	negative (0)	
ABS to Extractable Nuclear Ag;SCL-70,Serum		
SCL-70iGg Ab	NEG	
PM-SCL-Ab	neg(0)	
ABS to Extractable N Ag JO-1,Serum		
JO1-Abs	negative (0)	
ABS TO EXTRACTABLE NA(ANA BLOT),Serum		
PCNA Ab's	negative(0)	

Nucleosome Ab	neg(0)
AMA-M2 Ab	negative(0)
RibosomalP Abs)	negative(0)
Anti Phospho lipid IGG Ab's	
APL IGG Ab's ,Serum	2.67 nor-<12 Equiv:12.0-18.0 Pos ;>18

At that time she had extreme weakness of right upper and lower limb with slurring of speech. We started her on 60units iv enoxaprin for 3 days and then tab Deblexa(dabagatrin) 150mg daily. In the meantime we got her baseline CBC that revealed low haemoglobin and platelets suppressed till 70,000/cumm, besides high CRP ,LDH although D-Dimer was normal and COVID was negative. Besides these her TFT was normal but antithyroid antibodies were raised.With iv enoxaprin and above treatment improvement started occurring in limb movements and benefit in slurring of speech. LFT /RFT were within normal limits along with normal HIV/HCV / HBsAg /RT PCR for COVID.

25/3/21 Hb -8.8gm
TLC-5800 /cumm
DLC-P68,L25,M5E2M0B0
MCH 20.8
Plt count-70,000 lc/cumm (1.5-2.5 lakh/cumm
25/3CRP 21.16mg/dl(<0.6MG/DL
25/3DDimer 0.04 µg/ml
25/3LDH-437 µ (135-214)
28/3 Serum Ferritin 26.3ng/ml(10-291
20/3 Serum insulin PPInsulin -35.6mu/l(22-79)
20/3T3-117.59(60-181)
Tt4-8.374.6-10.9)
TSH-1.66 UIU/ML(0.35-5.50)
20/3Anti TPO Ab-67.07u/ml(<60)
ATG(anti thyroglobAb-18.05IU/ml(<60)
20/3HIV/HCV/HBsAg-Non Reactive
28/3LFT-SB--- 0.8mg/dl(0.2-1.2)----D—0.2mg/dl(0.1-0.3),I—0.6mg/dl(0.2-0.7)
SGOT(AST)----------25U/L(5-40)
SGPT(ALT)----------36 U/L(5-40)
ALP----------110U/L(50-126)
S Proteins -------6.8g/dl(5.5-8.0g/dl)----Alb----3.8g/dl(3.5-5.5),---Glob ----3.0g/dl(2.0-3.5 g/dl)
28/3RFT –BU----------31mg/dl(13-45)

S Creat----------1.0mg/dl(0.6-1.5 mg/dl)
Uric acid------5.9mg/dl(F-2.5-6.0mg/dl)
20/3/21GTT----------F-94mg
1 h-153mg
2h146 mg
(2h pp)-37(22-79iu/l)

USG on day 16-bilateral poly cystic ovary syndrome (PCOS) ovaries, uterus 44.1x37.1,ET 10.4mm,with a v small intramural fibroid 2x1.8mm Right ovary 28x18.5,Left ovary 38x28.5 mm, with a DF -18 mm, Injection enoxaprim was started at 60 units/day for 5 days s/c and then dablexa 100mg od – patient had great relief in her weakness in limbs with ability of lifting her foot which she had been dragging earlier and upper limb and slurring improved. Subsequently after getting full CBC ,CRP,LDH etc.

Subsequently she was given i/v methyl prednisolone with which she had 70% improvement in her limb movements and speech slurring and then oral wysolone 30 mg daily. After a week her limb movements were totally normal and speech improved. Haemoglobin improved to 11 gm, CRP, LDH became normal. Only abnormal parameter leftwas low platelets persisting to 70,000. Thus as per recommendations of ref 97-99 we started her on IV immunoglobulins and got her MRI to see what the exact findings were and decide if arterial,venous ormicroangiopathic stroke.

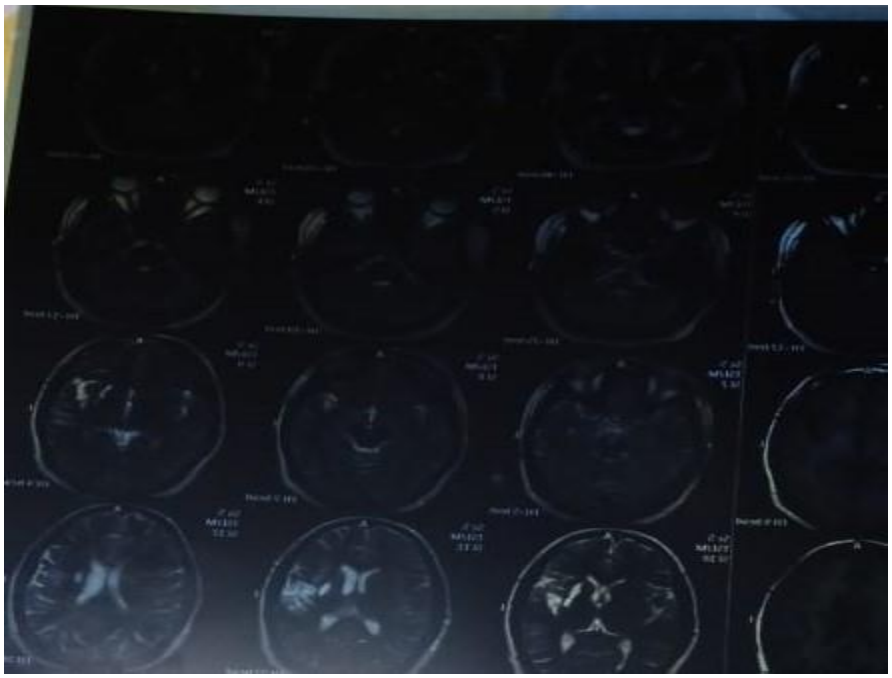

Figure 2: MRI of patient showing the CNS changes following stroke and asspociated rt parietal infarct,old It tempero parietal infarct in MCA territory

MRI Findings (**Figure 2)–** A small fresh non haemorrhagic lacunar infarct of 9x5mm size in right parietal cortex and shows restricted diffusion with reduced ADC Values. No haemorrhagic transformation is seen. No significant mass effect is seen A wedge shaped infarct is seen in left tempero parietal extent and is centred in relation to the left basal ganglia /capsular area and shows limiting gliosis with focal volume loss. A few small T2W/FLAIR focal hyper intensities are seen in either centrum semiovale in periventricular as well as subcortical areas. Mild periventricular asymmetrical gliosis is seen. Cerebellar hemispheres ,brain stem, pituitary gland /parasellar areas are normal. ventricular axis is normal.Midline septum is undisplaced. Visualized cranial nerves are normal CSF is unremarkable. Various flow voids are normal.

Impression

Small fresh lacunar infarct in right parietal cortex Large old infarct in left MCA territory ETAT LACUNAIRE. ETAT CRIBLET MILD periventricular asymmetrical Ischaemic demyelination > Mild changes secondary to microangiopathy in the background. Since she got a withdrawl bleeding and husband was leaving for Dubai we started her ovulation induction with CC on day 2 as patient is very keen for a live child and dablexa was omitted and shifted to iv enoxaprin and is under follow up.

Discussion

Thus our case represents the 13% quoted earlier of aPL positive patients that present with a stroke[11], which further belongs to the category of severe one from obstetrical point of view belonging to group 4.4 and 4.5 having had a 3rd trimester with history of this thrombotic attack where second hit came from Oral Contraceptives(OC's) introduction that is a known cause of precipitating a thrombotic episode and contraindicated in such patients having a history of recurrent pregnancy losses along with positive one of the APS antibodies (like LA positive in our patient, besides all viral infections ruled out like HIV/Covid [SARS CoV2]) as well as carrying a poor prognosis from obstetric point of view as in ref [81]following cerebral ischaemic events with future risks of preeclampsia ,preterm labour high. Further our pt has evidence of other autoimmune event from presence of TPO antibodies. Our patient responded fully after 4 mths of onset to besides LDA, LMWH, methyl prednisolone, iv immunoglobulins as utilized for CAPS as per 14th-16th task force recommendations along with ref [97-99]. Further would need LDP,LMWH through out pregnancy till 34-36 wks, temporarily omitted immediately before intrapartal events but restarted at post partal period in view of preventing thromboembolic events PP.Further low dose thyoxine would need to be added in view of positive TPO antibodies, close monitoring with counseling of the predicted poorer prognosis and be prepared to tackle CAPS or any such event.

References

1.Kulvinder Kochar Kaur, Allahbadia GN, Mandeep Singh.Succesful pregnancy Outcomes following use of Enoxaprin in recurrent pregnancy loss without APL Antibodies-Report of 2 cases.Int J Fam Commun Med 2017;1(3):00018.DOI:10.15406/ijfcm 2017.01,00018.

2.Kulvinder Kochar Kaur, Allahbadia GN, Mandeep Singh.An overview of Therapeutic Management of recurrent Pregnancy Loss.J Gynaecol 2017:2(3):000144.

3.Kulvinder Kochar Kaur, Allahbadia GN, Mandeep Singh.Need for treatment of antithyroid antibodies in recurrent Pregnancy Loss.ECGY 2020.

4.Kulvinder Kochar Kaur, Allahbadia GN, Mandeep Singh.Role of heparin in recurrent implantation failure –W M 2017.

5.Giannakopoulos B,Krilis SA.The pathogenesis of the Antiphospholipid syndrome.N Engl J Med 2013;368:1033-1044.

6.Schreiber K,Sciascia S,DeGroor PG,Devrees K,Jacobsen S,Ruiz –Irastorza Getal. Antiphospholipid syndrome.Nat Rev Dis Primers 2018;4:17103.

7.De Jesus GR ,Agmon –Levin N,Andrade CA,Andreoli LA,Chighizola CB,Porter TF, etal.14th International Congress on Antiphospholipid antibodies Task Force on Obstetric Antiphospholipid syndrome.Autoimmun Rev 2014;13:795-813.

8.Abreu MM,Danowski A,Wahl DG,Amigo MC,Tektonidou M,Pacheco MS, etal.The relevance of 'non criteria" clinical manifestations of Antiphospholipid syndrome: 14th International Congress on Antiphospholipid antibodies Task Force on Antiphospholipid syndrome Clinical Features. Autoimmun Rev 2015;14:401-414.

9.Cervera R,Bucciarelli S,Plasin MA,Gomez-Puerta JA,Plaza J,Pons Estel G, etal. Catastrophic Antiphospholipid syndrome(CAPS),:Descriptive analysis of a series of 280 patients from the "CAPS Registry ".J Autoimmun 2009;32:240-45.

10.Duarte Garcia A,Pham MM,Crowson CS,Amin S,Moder KG,Pruthi RK, etal.The epidemiology of Antiphospholipid syndrome,a population based study .Arthritis Rheumatol 2019;71:1545-52.

11.Durcan L,Petri M,Ricard Cervera GE,Munther K.Chapter 2- epidemiology of the Antiphospholipid syndrome.Handbook of Systemic Autoimmune Diseases:2017;Elsevier ,17-30.

12.Miyakis S,Lockshin MD,Atsumi T,Branch DW,Brey RL, Cervera R, etal. International Consensus Statement on an update of the classification criteria for definite Antiphospholipid syndrome(APS) .J Thromb Haemost 2006;4:295-306.

13.Zuo Y,Shi H, Knight JS. Antiphospholipidsyndrome:A Clinical perspective .Chinese Med J 2020;133(8)929-40.

14.Allen KL,Fonseca FV,Betapudi V,Willard B.Zhang J,McCrae KR.A novel pathway for human endothelial cell activation by Antiphospholipid/ anti β2-glycoprotein -1 antibodies. Blood. 2012;119:884-93.

15.Permpikul P,Rao LV,Rapaport SI.Functional and binding studies of the role of prothrombin and β2-glycoprotein -1 in the expression of lupus anticoagulant activity. Blood 1994;83:2878-892.

16.Chen PP,Giles I. Antibodies to serine proteases in the Antiphospholipid syndrome.Curr Rheumatol Rep 2010;12:45-52.

17.Zhang J, McCrae KR.Annexin A2 mediates endothelial cell activation by Antiphospholipid/ anti β2-glycoprotein -1 antibodies. Blood. 2005;105:1964-969.

18.Sorice M,Longo A,Cappozzi A,Garofalo T,Misasi R,Alessandri C, etal. Anti β2-glycoprotein -1 antibodies induce monocyte releade of tumor necrosis factor alpha and tissue factor by signal transduction pathways involving lipid rafts. Arthritis Rheum2007;56:2687-697.

19.Shi T, Giannakopoulos B,Yan X,Yu P,Berndt MC,Andrews RK , etal. . Anti β2-glycoprotein -1 antibodies in complex with β2-glycoprotein -1 can activate platelets in a dysregulated manner via glycoproteinIb-IX-V. Arthritis Rheum2006;54:2558-567.

20.Pierangeli SS,Girardi G,Vega-Ostertag M, Liu X,Espinola RG,Salmon J. Requirement of activation of complement C3 and C5 for Antiphospholipid antibody mediated thrombophilia. Arthritis Rheum2005;52:2120-124.

21.Girardi G,Redecha P,Salmon JE.Heparin prevents Antiphospholipid antibody mediated fetal loss by inhibiting complement activation.Nat Med 2004;10:1222-226.

22.Chaturvedi S,Brodsky RA, McCrae KR. Complement in the pathophysiology of Antiphospholipid syndrome.Front Immunol 2019;10:449.

23.Arachchillage DRJ,Laffan M. Pathogenesis and management of Antiphospholipid syndrome. Br J Haematol 2017;178:181-195.

24.Van den Hoogen LL RossatoM,Lopes AP,Pandit A,Bekker CPJ,Fritsch –Stork RDE, etal. micro RNAs downregulation in plasmacytoid dendritic cells in interferon positive systemic lupus erythematosus and Antiphospholipid syndrome. Rheumatol ogy 2018;57:1669-674.

25.Teruel R, Perez-Sanchez C,Corral J,Herranz MT, Perez-Andreu V.Saiz E, etal. Identification of mi RNAs as potential modulators and tissue factor expression in patients with systemic lupus erythematosus and Antiphospholipid syndrome. J Thromb Haemost 2011;9:1985-992.

26.Perez-Sanchez C,Arias –de la Rosa I,Aguirre MA,Luque –Tevar M,Ruiz-Limon P,Barbarroja N, et al. Crculating micro RNAs as biomarkers of disease and typification of the athero thrombotic status in Antiphospholipid syndrome. Haematologica 2018;103:908-18.

27.Perez-Sanchez C, ,Aguirre MA, Ruiz-Limon P, Barbarroja N,Jimenez –Gomez Y, Arias -de la Rosa I, etal. Athero thrombosis associated micro RNAs in Antiphospholipid syndromeand systemic lupus erythematosus patients'.Sci Rep 2016;6:31375.

28.Gupta S,Kaplan MJ.The role of neutrophils NETosis in autoimmune and renal diseases. Nat Rev Nephrol 2016;12:402-13.

29.Yalavarthy S,Gould TJ,Rao AN,Mazza LF,Morris AE,Nunez-Alvarez C , etal. Release of neutrophils extracellular traps by neutrophils stimulated with Antiphospholipid antibodies :a newly identified mechanism of thrombosis in the Antiphospholipid syndrome. Arthritis Rheumatol 2015;67:2990-3003.

30.Meng H,YalavarthyS,Kanthi Y, Mazza LF,Elfline MA,Luke CE, etal.In vivo role of neutrophils extracellular traps in Antiphospholipid antibody –mediated venous thrombosis. Arthritis Rheumatol 2017;69:655-67.

31.Sule G,Kelley WJ,Gockman K, YalavarthyS,Vreede AP,Banka AL, etal.Increased adhesive potential of Antiphospholipid syndrome neutrophils mediated by beta-2 integrin Mac 1 . Arthritis Rheumatol 2019;72:114-24.

32.Grenn RC, YalavarthyS,Gandhi AA,Kazaaz NM, Nunez-Alvarez C ,Hernandez-Ramirez D, etal. Endothelial progenitor dysfunction associates with atype1 interferon signature in primary Antiphospholipid syndrome.Ann Rheum Dis 2017;76:450-57.

33.Palli E,KravvaritiE,Tektonidou MG. Type1 interferon signature in primary Antiphospholipid syndrome:clinical and laboratory associations. Front Immunol 2019;10:487.

34.Knight JS,Meng H,Coit P, Yalavarthy S, Sule G, Gandhi AA, etal.Activated signature of Antiphospholipid syndrome neutrophils reveals potential therapeutic targets.JCI Insights 2017;2:e93897.

35.Ali RA, Gandhi AA, Meng H, Yalavarthy S, Vreede AP,Estes SK, etal.Adenosine receptor agonism protects against NETosis and thrombosis. In Antiphospholipid syndrome. Nat Commun2019;10:1916.

36.Samudra AN,Dwuyer KM,Sehan C,FreddiS,Murray-Segal L,Nikmour M, etal. CD39 and CD73 activity are protective in a mouse model of Antiphospholipid antibody –induced miscarriages.J Autoimmun 2018;88:131-38.

37.Barbhaiya M,Erkan D. Primary thrombosis prophylaxis in Antiphospholipid syndrome positive patients:where do we stand? Curr Rheumatol Rep 2011;13:58-69.

38.Crowther M,Legault KJ,Garcia DA, Tektonidou MG,Ugarte A,Bruce JN, etal.Prevention and treatment of thrombotic An tiphospholipid syndrome. Antiphospholipid syndrome Current research highlights ,Clincal Insights 2016 ;Springer International Publishing ,223-233.

39.Abdel –Wahab N,Lopez-Olivo MA,Pinto-Patarroyo GP,Suarez –Almazor ME. Systematic review of case reports of Antiphospholipid syndrome following infection.Lupus 2016;25:1520-531.

40.Vila P,Hernandez MC,Lopez-Fernandez MF,Battle J. Prevalence, follow up and Clincal significance of anticardiolipin antibodies in normal subjects . Thromb Haemost1994;72:209-13.

41.Pengo V,Tripodi A,Reber G,Rand JH,Oriel TL,Galli M, etal.Subcommittee on Lupus Anticoagulant/ Antiphospholipid antibody of the Scientific and Standardisation committee of the International Society of Thrombosis and Haemostasis. J Thromb Haemost 2009;7:1737-40.

42.Bertolaccini ML,Amengual O,Andreoli L,Atsumi T,Chighizola CB,Forastiero R, etal. International Congress on Antiphospholipid antibody Task Force .Report on Antiphospholipid syndrome laboratory diagnostics and trends . Autoimmun Rev 2014;13:917-30.

43.Bertolaccini ML,Amengual O,Artim –Eser B, Atsumi T,De Groot PG, De Laat B,Erkan D,Lockshin MD, etal. Clincal and prognostic significance of non 'criteria Antiphospholipid antibody tests. Antiphospholipid syndrome Current research highlights ,Clincal Insights 2016 ;Springer International Publishing ,223-233.

44.Garcia D, Erkan D.Diagnosis and management of the Antiphospholipid syndrome. N Engl J Med 2018;378:2010-2021.

45.Giron-GonzalezJA, Garcia del Rio E,Rodriquez C, Rodriquez-Martorelli J,Serrano A. Antiphospholipid syndrome and asymptomatic carriers of Antiphospholipid antibody : prospective analysis of 404 individuals. J Rheumatol 2004;31:1560-567.

46.Ruffatti A, del RossT,Ciprian M,Bertero MT,Sciascia S,Scarpato S, etal.Risk factors for the first Thrombic event in Antiphospholipid antibody carriers:a prospective multicentre prospective study. Ann Rheum Dis 2011;70:1083-1086.

47.Pengo V, Ruffatti A,Legnani C,Testa S,Fierro T,Marongiu F, etal.Incidence of a first Thrombic event in asymptomatic carriers of high risk Antiphospholipid antibody profile :a multicentre prospective study. Blood. 2011;118:4714-718.

48.Erkan D.,Harrison MJ,Levy R,Peterson MG,Petri M,Sammaritano L, Lockshin MD, etal. Aspirin for primary thrombosis prevention in the Antiphospholipid syndrome:a randomized,double blind , placebo controlled trial in asymptomatic Antiphospholipid antibody individuals. Arthritis Rheum2007;56:2382-391.

49.Erkan D,Yazicini Y, Peterson MG ,Sammaritano L, Lockshin MD.A cross sectional study of Clincal Thrombic Risk factors and preventive treatments in Antiphospholipid syndrome. Rheumatology 2007;56:924-29.

50.Tektonidou MG,Laskari K,Panagiotakos DB,Mountsopoulos HM.Risk factors for thrombosis and primary thrombosis in patients with systemic lupus erythematosus with or without Antiphospholipid antibodies. Arthritis Rheum2009;61:29-36.

51.Hereng T,Lambert M,Hachulla E,Samor M,Dubucquoi S,Caron C, etal.Influence of aspirin on the Clincal outcomes of 103 Antiphospholipid antibodies –positive patients. Lupus 2008;17:11-15.

52.Bala MM,Paszek E,Lesniak W,Wloch-Kopec D,Jasinska K,Undas A.Anti platelets and anticoagulant agents for primary prevention of thrombosis in individuals with Antiphospholipid antibodies . Cochrane Database Syst Rev 2018;7:CD012534.

53.Whitlock EP,Burda BU,Williams SB,Girguis-Blake JM,Evans CB.Bleeding risks with aspirin use for primary prevention in adults :a systematic review for the US preventive services task force .Ann Intern Med 2016;164:826-35.

54.LiL,Geraghty OC,Mehta Z,Rothwell PM,Oxford Vascular S.Age specific risks,severity ,time course ,and outcomes of Bleeding on longterm Anti platelets treatment after vascular events :a population based cohort study .Lancet 2017;390:490-99.

55.Edwards MH,Pierangeli S,Liu X,Barker JH,Anderson G,Harris EN. Hydroxychloroquine reverses thrombogenic properties of Antiphospholipid antibodies in mice . Circulation 1997 ;96:4380-384.

56.Rand JH,Wu XX,Quinn AS,Chen PP,Hathcock JJ,Taatjes DJ. Hydroxychloroquine directly reduces the binding of Antiphospholipid antibody –beta2 glycoprotein I complexes to phospholipid bilayers . Blood 2008;112:1687-695.

57.Rand JH,Wu XX,Quinn AS,Ashton AW, Chen PP,Hathcock JJ, etal. Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by Antiphospholipid antibodies :evidence for a novel effect of an old antimalarial drug. Blood 2010;115:2292-299.

58.Erkan D,Unlu O,Sciascia S,Belmont HM,Branch DW,Cuadrado MJ, etal. Hydroxychloroquine in the primary thrombosis prophylaxis of Antiphospholipid antibody positive patients without systemic autoimmune disease. Lupus 2018;27:399-406.

59.Ding HJ,Denniston AK,Rao VK,Gordon C. Hydroxychloroquine related retinal toxicity. Rheumatol ogy 2016;55:957-67.

60.Danesh FR,Anel RL,Zeng L,Lomasney J,Sahai A,Kanwar YSImmunomodulatory effects of HMG-CoA reductase inhibitors .Ann Immunol Ther Exp 2003;51:139-48.

61.Ferrara DE,Liu X,Espinola RG,Meroni PL,Abukhalaf I.Harris EN, etal.Inhibition of the thrombogenic and inflammatory properties of Antiphospholipid antibodies by fluvastatin in an invivo animal model. Arthritis Rheum2003;48:3272-279.

62.LopezPedrera C,Ruiz-Limon P,Aguirre MA, Barbarroja N,Perez-Sanchez C,Buendia P, etal.Global effects of fluvastatin on the prothrombotic status of patients with Antiphospholipid syndrome. Ann Rheum Dis 2011;70:675-82.

63.Erkan D,Willis R ,Murthy VL,Basra G,Vega J, Ruiz-Limon P, etal.A prospective open-label study of fluvastatin on proinflammatory and prothrombotic biomarkers in Antiphospholipid antibody positive patients . Ann Rheum Dis 2014;73:1176-180.

64.Kearon C,Agneo W,Cannegieter SC,Cosmi B ,Geersing GJ,Kyrle P, etal. Categorization of patients as having unprovoked versus thromboembolism guidance from the SSC of ISTH. J Thromb Haemost 2016;14:1480-483.

65.Lim W, Crowther MA,Eikelboom JW. Management of Antiphospholipid syndrome: A Systematic review.JAMA 2006;295:1050-1057.

66.Ruiz –Irastorza G,Khamashta MA,Hunt MJ,Escudero A , Cuadrado MJ,Hughes GR.Bleeding and recurrent thrombosis in definite Antiphospholipid syndrome:analysis of a series 66 patients treated with oral anti coagulation to a target International normalized ratio of 3.5.Arch Int Med 2002;162:1164-169.

67.Crowther MA,Ginsberg JS,Julian J,Denburg J,Hirsch J,Douketis J, etal.A comparison of 2 intensities of warfarin for the prevention of recurrent thrombosis in patients with Antiphospholipid syndrome. N Engl J Med 2003;349:1133-1138.

68.Finazzi G,Marchioli L,Brancaccio V,Shinco P,Wisloff F,Musial J, etal.A randomized clinical trial of high intensity warfarin for the prevention of recurrent thrombosis in patients with Antiphospholipid syndrome. J Thromb Haemost 2005;3:848-53.

69.Tektonidou MG,Andreoli L,Limper M,Amoura Z, Cervera R,Costedoat-ChalumeauN, etal.EULAR recommendations for the management of Antiphospholipid syndrome in adults . Ann Rheum Dis 2019;78:1296-1304.

70.Jackson WG,Oromendia C, Unlu O, Erkan D,DeSanchio MT. Antiphospholipid syndrome Alliance for Clincal T, etal recurrent thrombosis in patients with Antiphospholipid antibodies and arterial thrombosis on anti thrombotic therapy .Blood Adv 2017;1:2320-324.

71.Cohen H,Ethymiou M,Gates C,Isenberg D. Direct Oral Anti coagulants for thromboprophylaxis in patients with for Antiphospholipid syndrome.Semin Thromb Haemost 2018;44:427-38.

72.Cohen H,Ethymiou M, Isenberg D.Use of Direct Oral Anti coagulants in Antiphospholipid syndrome. J Thromb Haemost 2018;16:1028-39.

73.Cohen H,Hunt BJ,Ethymiou M,Arachchillage DR,Mackie IJ,Clawson S, etal. Rivaroxaban versus warfarin to treat patients with thrombotic Antiphospholipid syndrome,with or without systemic lupus erythematosus(RAPS) :A randomized controlled,open-labelphase2/3, noninferiority trial. Lancet Haematol 2016;3:e426-36.

74.Pengo V,Denas G,ZoppelaroG,Jose SP,Hoxha A, Ruffatti A, etal. Rivaroxaban versus warfarin in high risk patients with Antiphospholipid syndrome. Blood 2018;132:1365-371.

75.Ordi-Ros J,Saez –Comet L, Perez-Conesa M,Vidal X,Riera Mestre,Castro-Salomo A, etal. Rivaroxaban versus Vitamin K antagonist in Antiphospholipid syndrome: A randomized noninferiority trial. Ann Int Med 2019;162:1164-169.

76.del RossT,Ruffatti A,Visentin MS,Tonello M,Calligaro A,Favaro M, etal. Treatment of 139 pregnancies in Antiphospholipid antibodies positive women not fulfilling the criteria for Antiphospholipid syndrome: a retrospective study . J Rheumatol 2013;40:425-29.

77.Rolnik DL,Wright D,Poon LC,O'Gorman N,Syngelaki A,De Paco Matallana C, etal.Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613-22.

78.Goel N,Tuli A,Choudhary R.The role of Aspirin versus Aspirin and heparin in case of recurrent abortions with raised Anticardiolipin antibodies.Med Sci Monit 2006;12:CR132-CR136.

79.Laskin CA,Spitzer KA,Clark CA, Crowther MA,Ginsberg JS,Hawkier GA, etal. Low Molecular Weight H eparin and Aspirin for recurrent pregnancyloss :results from the randomized controlled Hep ASAtrial. J Rheumatol 2009;36:279-87.

80.Rey E,Garneau P,David M,Gauthier R,Leduc L,Michon N, etal. Dalteparin for the prevention of recurrence of placental mediated complications of pregnancy in women without thrombophilia :a pilot randomized controlled trial. J Thromb Haemost 2009;7:58-64.

81.Fischer Betz R,Specker C,Brinks R,Schneider M. Pregnancy outcomes in patients with Antiphospholipid syndrome after cerebral ischemic events:an observational study. Lupus 2012;21:1183-189.

82.DeStefano V,Martinelli I,Rossi E,Battaglioli T,Za T,MannuccioMannucci P, etal.The risk of recurrent venous thromboembolism in Pregnancy and puerpuerium without antithrombotic prophylaxis. Br J Haematol 2006;135:386-91.

83.Erkan D,Aguiar CL,Andrade D, Cohen H, Cuadrado MJ,Danowski A, etal. 14th International Congress on Antiphospholipid antibodies: Task Force on Antiphospholipid syndrome treatment Trends.Autoimmun Rev 2014;13:685-96.

84.Kumar D,Roubey RA .Use of Rituximab in the Antiphospholipid syndrome. Curr Rheumatol Rep 2010;12:40-44.

85.Erkan D,Vega J,Ramon G,Kazora E, Lockshin MD. Apilot open label phase II trial of Rituximab for noncriteria manifestations of Antiphospholipid syndrome. Arthritis Rheum2013;65:464-71.

86.Girardi G,Berman J,Redecha P,Spruce L,Thurman JK,Kraus D, etal. Complement C5a receptors and neutrophils mediate fetal injury in the Antiphospholipid syndrome.J Clin Invest 2003;112:1644-654.

87.Guillot M,Rafat C,Buob D,Coppo B,Jamme M,Rondeau E, etal. Eculizumab for catastrophic Antiphospholipid syndrome:a case report and review of literature . Rheumatology 2018;57:2055-2057.

88.Eissner G,Multhoff G,Gerbitz A,Kirchner S,Bauer S,Haffner S, etal.Fludarabine induces apoptosis ,activation and allogeneity in human endothelial and epithelial cells: protective effect of defibrotide. Blood 2002;100:1365-371.

89.Bracht F,Schror K.Isolation and identification of aptamers from defibrotide,an experimental antithrombotic afent on fibrinolysis and blood prostanoids in man. Biochem Biophys Res Commun 1994;200:933-37.

90.Bianchi G,Barone D,Lanzarotti E,Tettamanti R,Porta R,Moltrasio D, etal. Defibrotide ,a single stranded polydeoxyribonucleotide acting as an adenosine receptor agonist . Eur J Pharmacol 1993 ;238:327-34.

91.Richardson PG,Corbacioglu S,Ho VT,Kernan NA,Lehman L,Maguire C, etal.Drug safety evaluation of Defibrotide.Expert Opin Drug Saf 2013;12:123-36.

92.Pescador R,Cappuzzi L,Mantovani M,Fulgenzi A,Ferrero ME. Defibrotide:properties and clinical use of a old/newdrug, VasculPharmacol 2013;59:1-10.

93.Bercoglu –O'RaiA, Erkan D,Asherson R. Treatment of catastrophic Antiphospholipid syndromewith Defibrotide,a proposed Vascular endothelial cell modulator . J Rheumatol 2002;29:2006-2011.

94.Richardson PG,Elias AD,Krishnan A,Wheeler C,Nath R,Hoppensteadt D, etal. Treatment of severe veno-occlusive disease with Defibrotide:compassionate use results in response without significant toxicityin a highrisk population. Blood 1998;92:737-44.

95.Garrido-Maraver J,Cordero MD,Oropesa-Avila , VegaAF,De la Mata M,Pavon AD etal.Clinical applications of Coenzyme Q10.Front Biosci 2014;19:619-33.

96.Perez-Sanchez C, ,Aguirre MA, Ruiz-Limon P, Abalos-A guilera MC,Jimenez –Gomez Y, Arias -de la Rosa I, etal. Ubiquinol effects on Antiphospholipidsyndrome prothrombotic profile:a randomized placebo controlled trial.Arterioscler Thromb Vasc Biol 2017;37:1923-932.

97.Sevim E,Willis R, Erkan D.Is there a role of immunosuppression in Antiphospholipidsyndrome . New diagnostic and treatment strategies in Antiphospholipidsyndrome.Am Soc Haematol 2019;426-32.

98.Lequalt K,Schunemann H,Hillis C,Yeung C,Akl A,Carrier M, etal. Mcmaster –Rare-Best Practice Clinical practice Guidelines on diagnosis and management of Catastrophic Antiphospholipidsyndrome .J of Thrombosis and Haemost 2018;16:1656-654.

99.Cohen H, Erkan D, Cuadrado MJ , Ali RA, Knight JS, Isenberg D etal. : 16th International Congress on Antiphospholipid antibodies Task Force on Antiphospholipid syndromeT reatment Targets. . Lupus 2020;2(12):1571-593.

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