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Antiphospholipid Syndrome: Changing Knowledge During the Time – The ”Four P” Pattern

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1. Past

When searching the history of antiphospholipid antibodies one must meet cornerstone in Graham Hughes's descriptions of antiphospholipid syndrome in his "Prosser-White Oration" to the British Society of Dermatology in 1983 (Hughes GRV; 1984). The main points of his lecture can be found in different publications (Hughes GRV; 1984, Hughes GRV; 1999, Khamastha MA; 2000) and they are still truthful although they have been expressed almost thirty years ago. He finished his own work (Hughes GRV 1980; Hughes GRV; 1983) and crowned also another authors' important publication and observations. Some of these should be mentioned like the presence of false positive Wasserman reactions and also presence of circulating coagulants in patients with systemic lupus erythematosus (Laurel BB, Nilsson IM; 1957), the association of such circulating anticoagulants with thromboses (Bowie EJW et al 1983) and term "lupus anticoagulant" designation (Feinstein DI, Rapaport SI; 1972). The publication concerning association of these autoantibodies with foetal losses (Boey ML, et al; 1983) or the article which was directed to laboratory diagnostics (Harris EN, et al; 1983) arose almost at the same time as the Hughes's syndrome description.

The next important milestone emerged in 1990 when three independent working groups described the role of β_2-glycoprotein I as a target antigen in antiphospholipid antibodies' action (Galli M, et al; 1990, Matsura E, et al; 1990, McNeil HP, et al; 1990). This discovery substantially changed point of view of many of the researchers and also clinical practisers in the topic and it led to research of β_2-glycoprotein I structure, function and confirmation of significance of its antibodies presence during the next years.

As the important fact in our knowledge in antiphospholipid antibodies presence has to be stressed that laboratory investigation of lupus anticoagulants bodies has been under a control almost from the earliest time of their "standard" guidelines formulation (Exner T, et al; 1991, Barna LK, Triplett DA; 1991). The same situation is true in other antiphospholipid antibodies' detection and the experts have been searching continuously the solution to this problem until nowadays. Descriptions of the clinical manifestation of antiphospholipid antibodies' presence accompanied by antiphospholipid syndrome's definition were created in patients with systemic lupus erythematosus in the late eightieths and early ninetieths

(Alacrón-Segóvia D, et al; 1989a, Alacrón-Segóvia D, et al. 1992) and the definition and description of primary and also catastrophic antiphospholipid syndrome (Asherson RA, et al. 1989, Alacrón-Segóvia D, et al; 1989b) arose at the almost same time. This effort had led to so call Sapporo criteria of antiphospholipid syndrome which were generally accepted and widely used for many years (Wilson WA, et al; 1998).

2. Presence

Let's start "presence" twenty years after the antiphospholipid syndrome's description with two really important publications by Monica Galli (Galli M, et al; 2003a, Galli M, et al; 2003b) which summarised association of different type of antiphospholipid antibodies and their clinical significance in patients based on meta-analyses. The international consensus statement for definition of catastrophic antiphospolipid was published at the same year (Asherson RA, et al; 2003) and it was based on agreement by international workshop (during the international congress on antiphospholipid antibodies at Taormina, Italy 2002). The information from these articles has retained its importance until now.

The antiphopholipid syndrome's definition changed after discussion which started in international congress on antiphospholipid antibodies at Syndey 2004 (Miyakis S, at al. 2006). This consensus statement also determined non-criteria manifestations of antiphospholipid antibodies like thrombocytopenia, nephropathy and cardiac valve disease or livedo reticularis.

The important debate concerning serological criteria occurred at the pages of Journal of Thrombosis and Haemostasis in years 2007-2009 (Swadzba J, et al; 2007, Ruffatti A, et al; 2008, Galli M, et al; 2008, Pengo V; 2008, Tripodi A; 2008, Swadzba J et at; 2009, Ruffatti A, et al; 2009). The main finding from this debate seemed to be recommendation that the "cut off" in anticardiolipin antibodies' testing should be defined separately for thrombotic risk assessment and for pregnancy complication (Rufatti A, et al. 2008) and confirmation of the fact that the highest risk of clinical manifestation of antiphospholipid syndrome depends on the "triple positivity" of antiphospholipid antibodies, which means presence of lupus anticoagulant, significant positivity of anticardiolipin antibodies IgG and anti- β_2-glycoprotein I antibodies. Recommendation for lupus anticoagulant detection was also updated recently (Pengo V, et al; 2009, Tripodi A; 2009). The whole laboratory diagnostic process has been summarised in important publications (Gianacopulous B, et al; 2009, Pengo V, et al. 2010, Roubey RAS; 2010) including clinical meaning and critical analysis of different results.

An attempt to summarise briefly current knowledge in pathophysiology of antiphospholipid antibodies' action is a real "mission impossible". The same is true for the attempt to only list important researchers on the field. The compact overview bring Giannakopoulos (Giannakopoulos B, et al; 2007) or Meroni (Meroni PL; 2008). The role of prothrombotic and proinflammatory phenotype of endothelial cells, monocytes and platelets via direct action of antiphosholipid antibodies has been summarised by Pierangelli (Pierangelli SS, et al;2006). The connection between antiphospholipid antibodies, complement and foetal losses has been described for the first time by Holers (Holers VM, et al; 2002) and this research led to next association with tissue factor's role (Redecha P, et al; 2007). The most recent knowledge in pathophysiology of antiphospholipid antibodies was

widely discussed at the 13th international congress on anthiphospholipid antibodies, which was held in April 2010 at Galveston, Texas, USA. The role of innate immunity was described by Rauch (Rauch J, et al; 2010). The role of tissue factor was summarised by Boles and Mackman (Boles J, Mackman N; 2010). The pathophysiology of β_2-glycoprotein I was discussed by Matsuura (Matsuura E, et al. 2010), the role of the receptor LRP8 by de Groot (de Groot PG, et al. 2010) and involvement of protein C pathway by Urbanus (Urbanus RT, de Last B; 2010). The annexin A5-mediated mechanism in pregnancy losses and thrombosis was clarified by Rand (Rand JH, et al. 2010). These are the most important but definitely not all publications concerning antiphospholipid antibodies pathophysiology at this congress.

3. Perspectives

The great progression of our knowledge in antiphospholipid antibodies, their action and clinical manifestation is attended by arising of new questions and problems to be solved. Some of these have been opened by Lockshin many years ago (Lockshin MD; 2000) and not all of them have been answered until now. Many different experts of various specialisations like investigators, animal models experts, laboratory diagnosis specialists, clinicians and epidemiologists assign a lot of important tasks. Some of them should be mentioned.

3.1 Other autoantibodies

Evidence is increasing that a lot of other autoantibodies could be found in patients with antiphospholipid syndrome and/or with another clinical manifestation of antiphospholipid antibodies (Shoenfeld Y, et al; 2008). What is their role and how they could be involved in antiphospholipd syndrome diagnose?

3.2 Other diagnostic tools

Some new diagnostic procedures, which seem to bring new information for antiphospholipid antibodies' positive patients, have been described recently. The first of all is evaluation of circulating antibodies against domain I of β_2-glycoprotein I (de Laat B, et al 2005, de Laat B, et al. 2009). The positive finding correlates with thrombotic and obstetric history in IgG type of these autoantibodies. Next example is ELISA detection of IgG phosphatidylserine-dependent antiprothrobmin antibodies which seem to be associated with antiphospholipid syndrome manifestation and also with lupus anticoagulant presence (Atsumi T, Koike T; 2010). The open question is also the meaning of finding of the presence of autoantibodies directed to phospholipid itself (Tebo AE, et al. 2008). These examples belong to the most important discoveries which should be verified in daily clinical practice.

3.3 Therapy of antiphospholipid syndrome and antiphospholipid antibodies presence

The standard approach of the management of the antiphospholipid syndrome's manifestation has been described and accepted widely (Derksen RHWM, de Groot PG; 2010, Cervera R, et al; 2010). Other thing is primary prophylaxis of thromboembolic event in patient with asymptomatic course. Some recommendation but also controversy information in this field exist (Erkan D, et al; 2007, Metjian A, Lim W; 2009), but these patients' management has been considered as the open question until now. The new approaches with new directions which need to prove their action are under investigation. Some of new

antithrombotic drugs have proved their effectiveness in patient with thromboembolic disease when they were compared with vitamin K antagonists. The direct oral thrombin inhibitor dabigatran has a predictable anticoagulant effect and its safety profile is similar to that of warfarin (Schulman S, et al; 2009). Also rivaroxaban, an oral factor Xa inhibitor offers a simple, single-drug approach to the treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation (Bauersachs R, et al as the Einstein Investigators; 2010). These drugs are fixed-dose oral agents which do not appear to require routine laboratory monitoring and they may have a potential role in the management of patients in certain clinical manifestation of antiphospholipid syndrome. Among patients with acute venous thromboembolism approximately 10% have antiphospholipid antibodies and therefore it is likely that those patients were included in the study population in the dabigatran and rivaroxaban trials (Cohen H, Machin SJ; 2010). The potential advantages of these drugs in antiphospholipid antibodies positive patients have to be mentioned. The first of all is well known complicated laboratory monitoring in vitamin K dependent oral anticoagulant in the cases of lupus anticoagulants presence (Tripody A, et al; 2001). The second reasons which could favourite the new antithrombotic drugs is the fact that warfarin failures more frequently in secondary prevention in venous thromboembolisms in antiphospholipid antibodies than in other indications (Ames PRJ, et al; 2005, Wittkowsky AK, et al; 2006, Kearon C, et al; 2008).

Another approaches which could be involved in antiphospholipid antibodies positive persons management in future is potential immunomodulatory effect of some drugs. There are involved for example tissue factor up-regulation's inhibition, nuclear factor κB up-regulation's inhibition, p38 mitogen activated protein kinase up-regulation's inhibition, role of hydroxychloroquine, statins, anti-C5 monoclonal antibodies action or those against the lymphocytes bearing CD 20 receptor (rituximab) and other therapeutic modalities which role is supported only by animal models or only by episodic experiences in human (Pierangeli SS, Erkan D; 2010).

Vitamin D inhibits proinflamatory processes by suppressing the enhanced activity of immune cells that take part in autoimmune reactions. Shoenfeld Y, et al. intend to determine basal levels of vitamin D in patient with antiphospholipid syndrome and to identify those who require vitamin D supplementation, and to establish the therapeutic dose (Arnson Y, et al; 2007, Rotar Z, et al; 2009).

3.4 Other point of interest for the future

Future direction for antiphospholid syndrome research should concern some more opened questions. In aetiology of antiphospholipid antibodies the problems of infections, tumours, drugs and genetic predisposition could be involved. The meaning and managing of clinical manifestations associated with antiphopsholipid antibodies presence in which thromboembolic events are not suppose to be involved in clinical course also remains to be established (Shoenfeld Y, et al; 2008).

The next directions of the investigation at the field should be directed in paediatric patients. It includes newborns born to antiphospholipid antibodies positive mothers and their long-term clinical and immunological follow-up, paediatric antiphospholipid syndrome registry and clinical and laboratory differences between paediatric and adult patient with antipphospholipid syndrome (Rotar Z, et al; 2009, Avcin T, Silverman ED; 2007).

The really open field for next investigation seems to be mechanisms of antiphospholipid antibodies generation and action. The questions concerning why they occur or not, which pathways could be involved in their generation and next action, what are predisposing risk factors for their formation and clinical manifestation and many other still waiting for their solution.

4. Persons

It has been mentioned before and it will be mentioned once again later in this book that the problem of antiphospholipid antibodies and their effect really need interdisciplinary approaches. The leading persons in discovery of current knowledge of antiphospholipid antibodies and their action, clinical manifestation, detection and management are listed at the references of this chapter bellow, they belong to contributors of the next chapters of this book or they are mentioned in the references in these chapters. But, it should be stressed out, that persons themselves, theirs' contributions and publications, imagine and experiences and their willingness to share their knowledge are necessary requirements which could lead to important progress at the topic.

5. References

Alacrón-Segóvia D, Deléz M, Oria CV, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A perspective analysis of 500 consecutive patients. Medicine 1989a; 68: 353-365

Alacrón-Segóvia D, Sánches_Guerrero J. Primary antiphospholid syndrome. J Rheumatol 1989b; 16: 768-772

Alacrón-Segóvia D, Peréz-Vézquez ME, Villa AR, et al. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. Sem Arthr Rheumat 1992; 21: 275-285

Ames PRJ, Ciampa A, Margaglione M et al. Bleeding and re-thrombosis in primary antiphospholipid syndrome on oral anticoagulation. Thromb Haemost 2005; 93: 694-699.

Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic consideration. Ann Rheumat Dis 2007; 66: 1137-1142

Asherson RA, Khamashta M, Ordi-Ros J. The "primary" antiphospholipid syndrome. Major clinical and serological features. Medicine 1989; 68: 366-375

Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992; 19: 508-512

Asherson RA. Catastrophic antiphospholipid syndrome. International consensus statement on classification criteria and treatment guidelines. Lupus 2003; 12: 530-534

Atsumi T, Koike T. Antiprothrombin antibody: why do we need more assays. Lupus 2010; 19: 436-439

Avcin T, Silverman ED. Antiphospholipid antibodies in pediatric systemic lupus erythematosus and the antiphospholipid syndrome. Lupus 2007; 16: 627-633

Barna LK, Triplett DA. A report of the first international workshop for lupus anticoagulant identification. Clin Exp Rheumatol 1991; 9: 557-567

Bauersachs R, Berkowitz SD, Brenner B, et al as "The Einstein investigators". Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499-2510

Boey ML, Colaco CB, Gharavi AL, et al. Thrombosis in SLE: striking association with the presence of circulation lupus anticoagulant. BMJ 1983; 287: 1023

Boles J, Mackman N. Role of tissue factor in thrombosis in antiphospholipid antibody syndrome. Lupus 2010; 19: 370-378

Bowie EJW, Thompson JH jr, Pascuzzi CA, Owen CA jr. Thrombosis in systemic lupus erythematosus despite circulation anticoagulants. J lab Clin Med 1963; 62: 416-430

Cervera R, on behalf of the "CAPS registry project group". Catastrophic antiphospholipid syndrome (CAPS): update from the "CAPS Registry". Lupus 2010; 19: 412-418

Derksen RHWM, de Groot PG. Towards evidence-based treatment of thrombotic antiphospholipid syndrome. Lupus 2010; 19: 470-474

Cohen H, Machin SJ. Antithrombotic treatment failures in antiphospholipid syndrome: the new anticoagulants? Lupus 2010; 19: 486-491

Erkan D, Harrison MJ, Levy R et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome. Arthrit Rheumat 2007; 56: 2382-2391

Exner T, Triplett DA, Taberner D, Machin SJ. Guidelines for testing and revised criteria for lupus anticoagulants. SSC subcommittee for the standardization of lupus anticoagulants. Thromb and Haemost 1994; 65: 320-322

Feinstein DI, Rapapport SI. Acquired inhibitors of blood coagulation. Prog Hemost Thromb 1972; 1: 75-95

Galli M, Comfurius P, Maassen C, et al. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990; 335: 1544-1547

Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003a; 101: 1827-1832

Galli M, Luciani D, Bertolini G, Barbui T. Anti-β_2-glycoprotein I, antiprothrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome. Blood 2003; 102: 2717-2722

Galli M, Reber G, de Moerloose P, deGroot PG. Invitation to a debate on the serological criteria that define the antiphopsholipid syndrome. J Thromb Haemost 2008; 6: 399-401.

Giannakopoulos B, Passam F, Rahgozar S, Krilis SA. Current concepts on the pathogenesis of the antiphospholipd syndrome. Blood 2007, 109; 422-430

Giannakopoulos B, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. Blood 2009; 113: 985-994

De Groot PG, Derksen RHWM, Urbanus RT. The role of LRP8 (ApoER2') in the pathophysiology of antiphospholipid syndrome. Lupus 2010; 19: 389-393

Harris EN, Gharave AE, Boey ML, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in SLE: Lancet 1983; 2: 1211-1214

Holers VM, Girardi G, Mo L, et al. C3 activation is required for anti-phospholipid antibody-induced fetal loss. J Ex Med 2002; 195: 211-220

Hughes GRV. Central nervous system lupus-diagnosis and treatment. J Rheumatol 1980; 7: 405-411

Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. BMJ 1983; 287: 1088-1089

Hughes GRV. Connective tissue disease and the skin: the 1983 Prosser-White oration. Clin Exp Dermatol 1984; 9: 535-544

Hughes GRV. Hughes' syndrome: The antiphospholipid syndrome. A historical view. Lupus 1998, Suppl. 2: S1-S4

Kearon C, Julian JA, Kovacs MJ et al. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood 2008; 112: 4432-4436

Khamastha MA. Hughes Syndrome: History. In Khamastha MA (Ed): Hughes Syndrome: Antiphospholipid syndrome. Springer-Verlag London Berlin Heidelberg 2000; 3-7

Lockshin MD. Prognosis and future directions. In HKhamashta MA (Ed). Hughes syndrome. Antiphospholipid syndrome. Springer-Verlag London 2000: 459-462

de Laat B, Derksen RHWM, Urbanus RT, de Groot PG. IgG antibodies that recognize epitope Gly40-Arg43 in domain I of β_2-glycoprotein I cause LAC and their presence correlates strongly with thrombosis. Blood 2005; 105: 1540-1545.

de Laat B, Pengo V, Pabinger I, et al. The association between circulating antibodies against domain I of beta2-glycoprotein I and thrombosis.an international multicenter study. J Thromb Haemost 2009; 7: 1767-1773

Laurel BB, Nilsson IM. Hypergamaglobulinaemia, circulating anticoagulant and biologic false positive Wassermann reactions. J Lab Clin Med 1957; 49: 694-707

Matsuura E, Igarashi Y, Fujimoto M, at al. Anticardiolipin cofactor(s) and differential diagnosis of autoimmune disease. Lancet 1990; 336: 177-178

Matsuura E, Shen L, Matsunami Y, et al. Pathophysiology of β_2-glycoprotein I in antiphospholipid syndrome. Lupus 2010; 379-384

McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Anti-phospholipid antibodies are directed a complex antigen that includes a lipid-binding inhibitor of coagulation. Proc Natl Acad Sci 1990; 87: 4120-4124

Meroni PL. Pathogenesis of the antiphospholipid syndrome. An additional example of the mosaic of autoimmunity. J Autoimmunity 2008; 30: 99-103

Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on update of an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295-306

Pengo V. A contribution to the debate on the laboratory criteria that define the antiphospholipid syndrome. J Thromb Haemost 2008; 6: 1048-1049.

Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009; 7: 1737-1740

Pengo V, Banzato A, Bison E, et al. Antiphosholipid syndrome: critical analysis of the diagnostic path. Lupus 2010; 19: 428-431

Pierangeli SS, Chen PP, Gonzalez EB. Antiphospholipid antibodies and the antiphospholipid syndrome: an update on treatment and pathogenic mechanisms. Curr Opin in Hematology 2006; 13: 366-375

Pierangeli SS, Erkan D. Antiphospholipid syndrome treatment beyond anticoagulation: are we there yet. Lupus 2010; 19: 475-485

Rand JH, Wu X-X, Quinn AS, Taatjes DJ. The annexin A5-mediated pathogenetic mechanism in antiphospholipid syndrome: role in pregnancy losses and thrombosis. Lupus 2010; 19: 460-469

Rauch J, Dieudé M, Subang R, Levine JS. The dual role of innate immunity in the antiphospholipid syndrome. Lupus 2010; 19: 347-353

Redecha P, Tilley R, Tencati M, et al. Tissue factor: a link between C5a and neutrophil activation in antiphospholipid antibodiy induced fetal injury. Blood 2007; 110: 2423-2431

Roubey RAS: Risky business: the interpretation, use, and abuse of antiphospholipid antibodies tests in clinical practice. Lupus 2010; 19: 440-445

Rotar Z, Rozman B, de Groot PG, et al. Sixth meeting of the European Forum on antiphospholipid antibosies. How to improve the understanding of the antiphospholipid syndrome. Lupus 2009; 18: 53-60

Ruffatti A, Olivieri S, Tonello M, et al. Influence of different IgG anticardiolipin antibody cut-off values on antiphospholipid syndrome classification. J Thromb Haemost 2008; 6: 1693-1696.

Ruffatti A, Pengo V. Antipospholipid syndrome classification criteria: comments to the Letter of Jakub Swadzba and Jacek Musial. J Thromb Haemost; 7: 503-504

Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361: 2342-2352

Shoendfeld Y, Twig G, Katz U, Sherer Y. Autoantibody explosion in antiphospholipid syndrome. J Autoimmunity 2008a; 30: 74-83

Shoenfeld Y, Meroni PL, Cervera R. Antiphospholipid syndrome dilemmas still to be solved: 2008 status. Ann Rheumat Dis 2008b; 67: 438-442

Swadzba J, Iwaniec T, Szczeklik A, Musial J. Revised classification criteria for antiphospholipid syndrome and the thrombotic risk in patients with autoimmune disease. J Thromb Haemost 2007; 5: 1883-1889.

Swadzba J, Musial J. Letters to the Editor. More on: The debate on antiphospholipid syndrome classification criteria. J Thromb Haemost 2009; 7: 501-502.

Tebo AE, Jaskowski TD, Phansalkar AR, et al. Diagnostic performance of phospholipid-specific assays for the evaluation of antiphospholipid syndrome. Am J Clin Pathol 2008; 129: 870-875.

Tripodi A, Chantaraggkul V, Clerici M, et al. Laboratory control of oral anticoagulant treatment by INR system in patient with antiphospholipid syndrome and lupus anticoagulant. Result of a collaborative study involving nine commercials thromboplastins. Br J Haematol 2001; 115: 672-678

Tripodi A. More on: criteria to define the antiphospholipid syndrome. J Thromb Haemost 2008; 6: 1049-1050.

Tripodi A. Testing for lupus anticoagulants: all that a clinician should know. Lupus 2009; 18: 291-298

Urbanus RT, de Laat B. Antiphospholipid antibodies and the protein C pathway. Lupus 2010; 394-399

Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification for definite antiphospholipid syndrome. Arthritis Rheumatol 1999; 42: 1309-1311

Wittkowsky AK, Downing J, Blackburn J, Nutescu E. Warfarin-related outcomes in patients with antiphospholipid antibody syndrome managed in an anticoagulation clinic. Thromb Haemost 2006; 96: 137-141

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