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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.

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