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Review

14th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome

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ABSTRACT

The 'Task Force on Catastrophic Antiphospholipid Syndrome (CAPS)' was developed on the occasion of the 14th International Congress on Antiphospholipid Antibodies. The objectives of this Task Force were to assess the current knowledge on pathogenesis, clinical and laboratory features, diagnosis and classification, precipitating factors and treatment of this condition in order to address recommendations for future research. This article summarizes the studies analyzed by the Task Force, its recommendations and the future research agenda.

Contents

1. Introduction

The 'Task Force on Catastrophic Antiphospholipid Syndrome (CAPS)' was developed on the occasion of the 14th International Congress on Antiphospholipid (aPL) Antibodies. The objectives of this Task Force were to assess the current knowledge on pathogenesis, clinical and laboratory features, diagnosis and classification, precipitating factors and treatment of this condition in order to address recommendations for future research.

The members of the Task Force included all the authors of this paper. During a pre-congress workshop in Rio de Janeiro, Brazil, on 18 September 2013, the members presented the current evidence in their area of expertise and provided relevant literature on it. An open discussion followed (both during the pre-congress workshop and during the elaboration of the manuscript), to reach consensus. Where data was limited or incongruent, expert opinion supplements

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the recommendations. This article summarizes the studies analyzed by the Task Force.

2. Pathogenesis

Although clinical findings are well defined, the pathological mechanisms of CAPS are less understood. Nonetheless, the close association between CAPS and classic antiphospholipid syndrome (APS) suggests the presence of possible overlapping mechanisms. However, it is still unclear why some patients will develop recurrent thrombosis mainly affecting large vessels (classic APS), while others develop rapidly recurrent vascular occlusions, predominantly affecting small vessels (CAPS). In 1998, Kitchens introduced the new concept of "thrombotic storm" to describe a peculiar event in the course of CAPS referred to the possible ability of vascular occlusion to trigger itself additional thrombosis [1]. According to such hypothesis, the author proposed that while clots continue to generate thrombin, fibrinolysis is decreased by an increase in plasminogen activator inhibitor (PAI) type-1 determining a consumption of the natural anticoagulant proteins such as protein C and antithrombin.

APS is considered to have a multifactorial etiopathogenesis and the involvement of both adaptive immunity and innate immunity, supported by the presence of a predisposing genetic background, is required [2]. An association between HLA class II genes and aPL production has been already described. Specifically, an association with several polymorphisms [HLA-DRB1*04, DRB1*07 (0701), DRB1*1302, DR53, DQB1*0301 (DQ7), *0302, and *0303] shows not only a predisposition to aPL production, but also a possible binding of peptides useful for T cells recognition mediated by HLA class II molecules [3,4]. Later on, other possible associations including HLA-DPB1 alleles [5], HLA-DM polymorphisms [6] or valine/leucine247 polymorphism of β2-glycoprotein I (β2GPI) [7] have been identified.

In association with the presence of a predisposing genetic background able to determine aPL production, the existence of a genetic thrombophilia may represent another possible predisposing risk factor for CAPS development. Specifically, this kind of predisposition includes a depression of the natural anticoagulant system, endogenous hypofibrinolysis (i.e. PAI-1 4G/5G, t-PA I/D), prothrombin G20210A mutation or a MTHFR C677T mutation [8]. In such condition, the presence of aPL may represent the "*first hit*" leading to an increase in the thrombophilic risk.

Nonetheless, the positivity of such antibodies is not sufficient to trigger the clot and the presence of an inflammatory hit, named the "*second hit*", is required. In fact, the presence of environmental trigger factors seems to be essential in CAPS development [9]. These trigger factors have been recognized in more than half of CAPS cases, mostly represented by infections (viral or bacterial) [9]. The presence of aPL has been identified in several infections confirming a potential relationship with APS pathogenesis [10]. During microvessels thrombosis an excessive release of different cytokines (especially interleukin IL-1, IL-6 and TNF) is commonly observed, a phenomenon that can occur during CAPS and that has been referred to as the "cytokine storm". This event is responsible for the development of a dramatic systemic inflammatory response syndrome (SIRS).

Cytokines are small secreted extra-cellular signaling proteins/peptides which regulate cell-mediated immune responses [11]. These molecules include interleukins, interferons, hematopoietic stimulating factors and tumor necrosis factors [12]. They are the key components of effector phase immunity.

There are no studies on cytokine involvement in CAPS because due to its rarity it is difficult to collect blood and serum samples during an episode of CAPS. Additionally, there is a lack of knowledge of physicians in intensive care units where most of these patients are admitted. However, there is indirect evidence that cytokines play a major role in CAPS.

There are two theoretical explanations for the clinical manifestations in CAPS: 1) manifestations dependent on the organs that are affected by the thrombotic events and extent of the thrombosis; and 2) manifestations related to the SIRS [13]. Cytokines seem to play a role in both the thrombotic manifestations and those relate to the SIRS.

Certainly, some nonthrombotic manifestations, particularly ARDS, are frequently encountered in both CAPS and sepsis. ARDS is known to be induced by pro-inflammatory cytokines including TNF-α, IL-1, IL-6, IL-18 and macrophage-migration inhibitory factor [14].

Moreover, in the sepsis model, proinflammatory cytokines are important in inducing a procoagulant effect. Coagulation pathways are initiated by lipopolysaccharide (LPS), inducing expression of tissue factor on mononuclear and endothelial cells [15]. There is some evidence that in CAPS, anti-β2GPI antibodies trigger an endothelial-signaling cascade comparable to that activated by LPS in sepsis [16].

The thrombophilic state in APS has been attributed to the induction of a proinflammatory and procoagulant endothelial cell phenotype resulting from anti-β2GPI binding to β2-GPI expressed on the endothelial cells. Anti-β2GPI binding has been shown to induce NF-κB translocation, leading to a proinflammatory endothelial cell phenotype (similar to that elicited by microbial products such as LPS in sepsis) and the production of proinflammatory cytokines [17]. The accelerated activation of this mechanism could possibly contribute to SIRS and thrombosis seen in CAPS patients.

As mentioned above, both adaptive immunity and innate immunity are involved in APS pathogenesis suggesting their participation in CAPS as well. Anti-β2GPI antibodies are the expression of the adaptive immune response and have a pro-thrombotic role through several mechanisms, including interference with natural anticoagulants (such as protein C and annexin V), inhibition of fibrinolysis, interference with cells of the coagulation cascade (such as endothelial cell perturbation, circulating monocytes and platelet activation), and by triggering complement activation [2].

Recently, other possible autoantigens have been supposed to take part to the pathogenic mechanisms of APS. Specifically, anti-vimentin/cardiolipin antibodies have been identified in patients with APS and a new possible role for vimentin, as a cofactor for aPL antibodies has been proposed [18]. On the other side, massive complement activation in the course of APS is the expression of the innate immune system involvement. Currently, we know that complement cascade, induced by aPL, is linked with pregnancy loss, fetal growth restriction and thrombosis. Complement C1q protein is significantly activated in patients with APS inducing the cascade onset with a further release of active fragments of the complement system leading to the amplification of the activation of monocytes, platelets or endothelial cells [19]. These fragments, such as C5a, were found to induce tissue factor expression on neutrophils, resulting in a modified prothrombin time [20]. These findings brought to the usage of targeted therapy against complement as a novel approach in the treatment of APS [21]. Tissue factor is another key initiator of the clotting cascade and aPLs were found to be able to induce its expression on monocytes, endothelial cells and platelets [22]. It has been demonstrated that patients with APS may have an increased β2GPI exposure on cell surface which leads to persistently high monocyte tissue factor expression [23].

Another key mechanism in classic APS as well as in CAPS is endothelial cell activation. There is strong evidence that, in the absence of other detectable traditional risk factors for atherosclerosis, aPLs perturb the endothelium by inducing vasculopathy and an endothelial pro-inflammatory/coagulant phenotype [24]. It has been recently demonstrated that receptors of innate immunity, such as TLR-4, are involved in endothelial cell activation following the binding of anti-β2GPI antibodies [25]. Such activation of TLR4 triggers IL-1 receptor-associated kinase phosphorylation and NF-κB translocation, promoting VCAM expression on endothelial cells and TNF-α release by monocytes [26].

In addition to the above-mentioned mechanisms, recent reports suggest a possible pathogenic role for oxidative stress. In fact, an increased oxidative stress in the course of APS has been observed. The oxidation determines the exposition of the critical epitope domain I