



Review

The physiopathology of the catastrophic antiphospholipid (Asherson's) syndrome: Compelling evidence

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ABSTRACT

Catastrophic antiphospholipid (Asherson's) syndrome (cAPS) was described in the past as a severe variant of the antiphospholipid syndrome (APS). Currently growing evidence suggests it is a unique condition. This statement is based on several clinical and physiopathological features that although not well understood define cAPS by itself. The remarkable features of cAPS are the presence of antiphospholipid antibodies (aPLAs) and microthromboses. Additional physiopathological features are the presence of anemia and thrombocytopenia, which are also often described in similar autoimmune conditions. A strong association with concomitant infection is thought to act as the main trigger of microthromboses in cAPS. Several theories have been proposed to explain these physiopathological features. Some of them suggest the possibility of molecular mimicry between components of infectious microorganisms and natural anticoagulants, which might be involved in the production of cross-reacting aPLAs in cAPS. Some genetic risk factors have also been suggested to be implicated in the onset of cAPS, however they have not been defined yet. Herein, we review the remarkable physiopathological features commonly described in cAPS hitherto. We concluded that although they are not completely understood, it is possible to differentiate them from similar conditions. Nevertheless further studies on these physiopathological mechanisms of the disease are needed.

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1. Introduction

Since the first description of the catastrophic antiphospholipid syndrome (cAPS) as an accelerated manifestation of microthromboses was published [1], an increasing number of patients with this antiphospholipid syndrome (APS)-related condition have been reported [2,3]. The incidence of cAPS represents less than 1% of the APS cases. However it is often associated with a high rate of mortality (i.e. 50%) usually as a consequence of multiorgan failure [2,3]. Specific clinical criteria for cAPS have been defined [4]. These criteria entail the evidence for thromboses of three or more organs, the histological finding of small vessel occlusion in at least one organ, the rapid development of clinical manifestations and a laboratory confirmation for the presence of antiphospholipid antibodies (aPLAs) [2,5]. Although clinical findings are well defined, the physiopathological mechanisms involved in this condition are less understood. Several theories have been proposed [6], but none

of them was clearly confirmed. Noteworthy a close association between cAPS with the classical "primary APS" suggests an overlapping physiopathological mechanism [7–9]. The development of microvascular thrombotic occlusions, thrombocytopenia, microangiopathic anemia and the presence of specific aPLAs such as anti-β2-glycoprotein-1 (anti-β2-GPI) [10] and anticardiolipin antibodies (aCL) are characteristic findings of patients with cAPS [2,4]. However, there are identifiable features allowing to make a distinction between the two conditions as well. An often history of "triggering" factors, rapid onset of multiorgan dysfunction syndrome, and the development of acute respiratory distress syndrome (ARDS) in almost 25% of patients have characteristically been described in cAPS [11]. Moreover a profound involvement of microthromboses characterizes cAPS as opposed to the mainly large vessels' occlusion in APS. Those intriguing and unclear physiopathological clues commonly described in cAPS made this condition an interesting topic to be discussed.

2. Pathophysiology of cAPS – the general picture

The physiopathological mechanisms involving cAPS are not clearly understood. Typically cAPS is an acute thrombotic

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microangiopathy affecting small-calibre blood vessels in multiple organs: 50% of cases involving the lungs, central nervous system, heart, kidney, skin and gastrointestinal tract. Atypical and unusual occlusive events involving the adrenal, pancreatic, spleen and testicular vessels have also been reported [2,10]. The characteristic physiopathological features of cAPS are summarized in Table 1. Several hypotheses have been proposed to explain this singular presentation. In 1998 *Kitchens* postulated that vascular occlusion itself triggers additional thrombosis, which was termed the “thrombotic storm” [12]. He proposed that clots continue to generate thrombin, fibrinolysis is depressed by an increase in plasminogen activator inhibitor type-1 (PAI-1), and there is a consumption of the natural anticoagulant proteins such as protein C and antithrombin. In 2000 *Meroni et al.* [13] pointed to the role of aPLAs in endothelial cell (EC) activation as a pathogenic mechanism of thrombosis in APS. In 2003, *Raschi et al.* furthermore explored the relation between aPLAs, particularly anti-β2-GPI and EC activation [14]. They suggested that anti-β2-GPI antibodies might mediate the activation of ECs, leading to either an alteration in the endothelial phenotype or a switch to a procoagulant microenvironment responsible for the thrombotic manifestations. This phenomenon is commonly denominated thrombosis mediated by antibodies [15]. An etiological explanation was proposed by *Asherson and Shoenfeld*, the theory of “molecular mimicry” [7]. It was derived from experiments in mice suggesting that peptides derived from β2-GPI, which are recognized by anti-β2-GPI antibodies, shared some amino-acid sequences with those found on membranes of diverse viruses, bacteria, and parasites [16,17]. It might explain the relationship that has been reported between infection and the presence of anti-β2-GPI antibodies in cAPS [12]. Thus, it seems that by molecular mimicry some infectious agents can induce the production of anti-β2-GPI antibodies which induce endothelial cells’ activation and coagulation [18,19].

3. The role of antibodies in cAPS and molecular mimicry

The presence of aPLAs constitutes one of the criteria for the diagnosis of cAPS and they are more often found in patients with microthromboses [4,20]. aPLAs induce the activation of ECs, as assessed by up-regulation of the expression of cell adhesion molecules, the secretion of cytokines, and an increased metabolism of prostacyclins in the blood stream [13,21]. Interestingly, some products derived from the metabolism of prostacyclins such as 6-keto-PGF1-α (metabolite of arachidonic acid) have been found raised in patients with APS, and are mainly related to the presence of microthromboses in several patients [21,22]. An alteration of the coagulation system has been reported in APS. The generation of antibodies against β2-GPI, which has been suggested to act as a natural anticoagulant on EC surface, is an important physiopathological feature of APS [2]. A procoagulant state is thought to be triggered by the binding of anti-β2-GPI antibodies to β2-GPI on

Table 1
Physiopathological features of cAPS.

Systemic microvascular thrombosis, mainly in solid organs
Microangiopathic anemia
Associated thrombocytopenia
Presence of aPLAs in high titres
Associated “trigger” factors, primarily infection – (molecular mimicry)
Rapid progression (less than a week)
SIRS
DIC
MOF

cAPS: catastrophic antiphospholipid syndrome; aPLAs: antiphospholipid antibodies; SIRS: systemic inflammatory response syndrome; DIC: disseminated intravascular coagulation; MOF: multiorgan failure.

the EC surface [23]. Similar mechanisms have been suggested regarding the interference of the normal regulatory functions of prothrombin, protein C, annexin V, and tissue factor in APS [24]. Although an association between the presence of aPLAs and the occurrence of microthromboses is well established, a “second hit” is needed for thrombosis to occur not only in APS, but mainly in cAPS [6]. In several studies anti-β2-GPI antibodies were shown to recognize peptides derived from β2-GPI, displaying a molecular mimicry with common components of bacteria and viruses, both at amino-acid sequence and conformational structure levels [15,25]. Such homology was suggested to represent the rationale for the possible infectious origin of the APS syndrome but also can be suggested for cAPS [7]. The mechanism of association between anti-β2-GPI antibodies and infection has been studied in some experiments showing that β2-GPI might activate the immune response via interaction with Toll-like receptors (TLRs) [13]. TLRs are single membrane receptors which recognize structurally conserved molecules broadly shared by pathogens but also distinguishable from host molecules [26]. The intracellular signaling is thought to be driven by the intracellular TLR domain via IRAK (IL-1 associated kinase), a process mediated by an adapter protein MyD88 (myeloid differentiation protein 88) [14]. The activation of IRAK induces the nuclear translocation of the nuclear factor NF-κB from the cytoplasm to the nucleus in ECs [26] (Fig. 1). This signal increases the production of proinflammatory cytokines (TNF-α, IL-1B, IL-6, IL-8) and procoagulant factors such as tissue factor (TF) and plasminogen activator inhibitor (PAI-1) [13]. Interestingly, anti-β2-GPI antibodies have been reported to induce the nuclear factor NF-κB translocation *in vitro*, resembling the mechanism evoked by the recognition of microorganisms by TLRs [27]. Noteworthy anti-β2-GPI antibodies can recognize some microbe molecules that might cross-link with TLRs [26,28]. In this regard, both human monoclonal IgM and polyclonal IgG anti-β2-GPI antibodies can induce an endothelial signal similarly to such one induced throughout TLR-4 receptor by infectious microorganisms [13]. Those findings suggest that anti-β2-GPI antibodies might initiate the activation of EC throughout the TLR-4 receptor, largely involved in the activation of the inflammatory cascade by lipopolysaccharide (LPS) [29].

4. The role of infection in the pathogenesis of cAPS

Infection has been reported as a preceding risk factor for cAPS onset [30,31]. This association is larger after compared to that one described in APS [32]. Among the precipitating risk factors according with the analysis of 250 patients from the “cAPS Registry” [33], infectious diseases were the remarkable triggering risk factors (22%). Additional studies reported that up to 60% of patients had developed cAPS following infection [6]. Specific infections have been reported; dengue, typhoid fever, urinary infection, and upper respiratory tract infection are the remarkable examples. As mentioned previously, the production of anti-β2-GPI can be induced by infectious agents present in the blood stream [16,25]. Interestingly, virus and bacteria share some amino-acid sequence homology to the binding site recognized by anti-β2-GPI antibodies on β2-GPI, and therefore they may induce the production of crossreactive anti-β2-GPI [34]. Noteworthy the manifestations of the systemic inflammatory response syndrome (SIRS) have been reported in patients with cAPS [35]. The clinical manifestations of ARDS, encephalopathy, and myocardial dysfunction in cAPS have been related to the development of SIRS [35]. It is now recognized that SIRS may arise both from septic and from non-infectious causes such as an autoimmune-mediated organ injury. Both sepsis and cAPS may be present as SIRS. Sepsis as a model of systemic inflammatory response to infection has been suggested to explain some overlap findings between the two entities [36]. cAPS

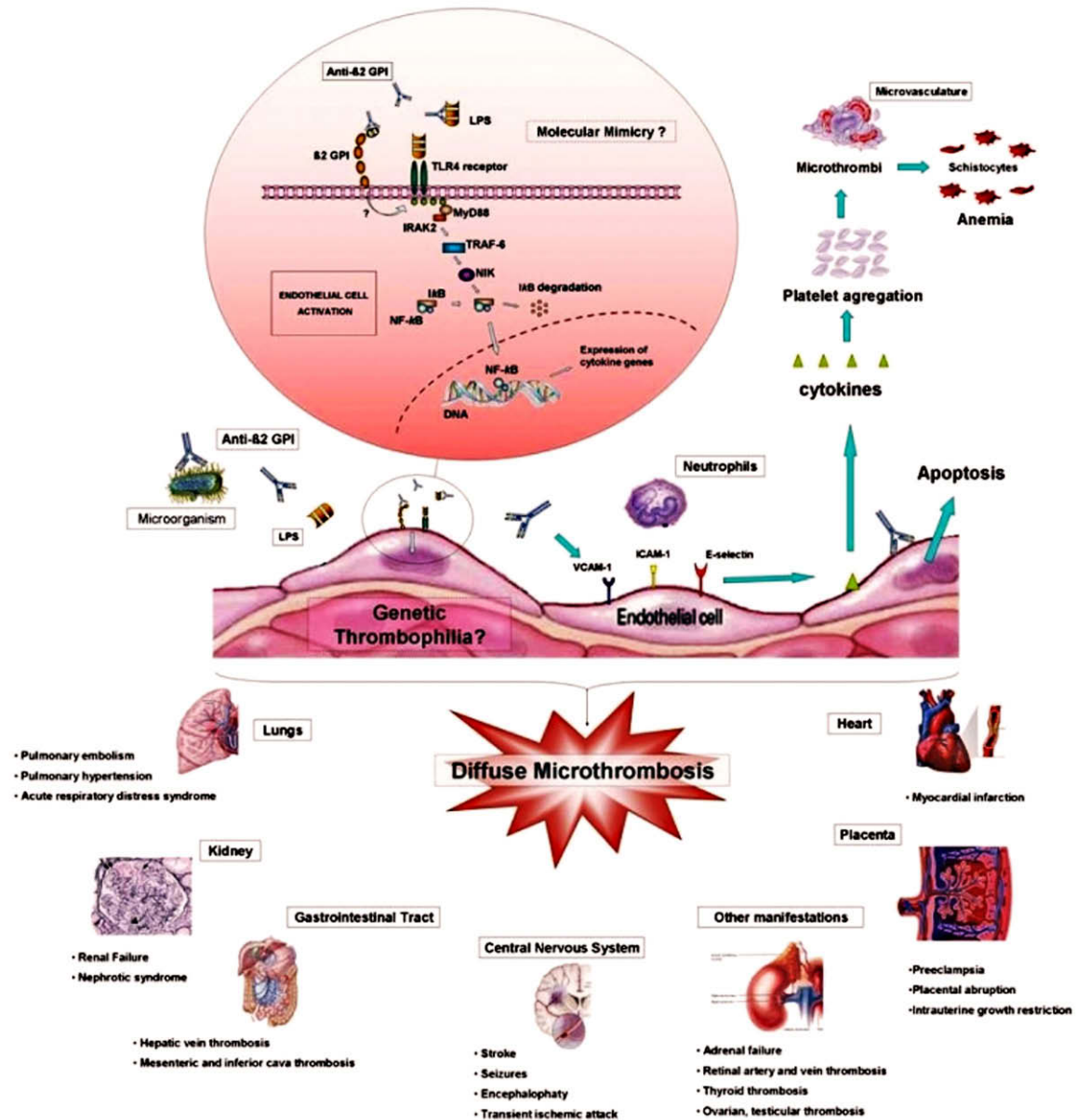


Fig. 1. Hypothetical model for the pathophysiological mechanisms in cAPS. The possibility of molecular mimicry between some molecular components of infectious agents and natural anticoagulants might be suggested as a model to explain the initial step in the activation of endothelial cells (ECs) in cAPS. The initial activation of ECs is thought to be triggered by the binding of antiphospholipid antibodies to ECs surface. The cascade of signal transduction events (NF- κ B) to the nucleus inside ECs is thought to be driven throughout TLR-4 receptor, which is mainly implicated in the recognition of infectious agents. This process is followed by the production of proinflammatory cytokines, an increased expression of cell adhesion molecules, platelet aggregation, anemia, induction of apoptosis of ECs, and the generation of diffuse microvascular coagulation, primarily in solid organs. Although the genetic risk factors associated in cAPS have not been defined at all, some evidence suggests that genetic thrombophilia might constitute the genetic background in the pathophysiology of cAPS.

resembles severe sepsis in its acute presentation with multiple organ dysfunction. Organ failure and severe sepsis are associated with sequestration and aggregation of neutrophils in renal blood vessels and large-scale infiltration in multiple organs, resulting in multiorgan involvement. But in contrast to sepsis, cAPS is strongly associated with the presence of anti- β 2-GPI antibodies. Interestingly, sepsis begins with the activation of host cells by recognition of LPS through TLRs, mainly by TLR-4. We mentioned previously that TLR-4 likely participates in EC activation mediated by anti- β 2-GPI antibodies in both APS and cAPS [13]. The activation and signaling throughout this receptor induces ultimately the switch to the production of proinflammatory cytokines (TNF- α , IL-1 β and IL-6) [36]. Moreover the model of sepsis might also explain the

development of microthromboses, the main feature of cAPS [34,36]. Those findings remark also that infection may play a pivotal role in the pathogenesis of cAPS.

5. Activation of endothelial cells in the microvasculature

cAPS was hypothesized to be associated with ECs activation as a result of antigen–antibody reactions on ECs surface. In one study, antibody activation of ECs was observed only in patients with aPLAs in comparison to patients with idiopathic thrombocytopenia (ITP) [37]. In another study assessing the *in vivo* formation of thrombus in mice, the presence of aPLAs correlated well with an increased thrombus formation, and significant higher expression of vascular

cell adhesion molecule-1 (VCAM-1) [38]. An additional study reported a high frequency of livedo reticularis preceding the arterial occlusions and the subsequent development of ischemic necrosis and amputation of limbs/digits (cAPS), in patients positive for antiphospholipid antibodies [39]. In addition a complex gene expression of multiple proinflammatory cytokines, and pro-thrombotic proteins in response to the binding of anti-β2-GPI antibodies to ECs has been reported in studies *in vitro* [40]. Those findings suggest that in cAPS, the activation of ECs might be driven by the binding of aPLAs.

6. Microvascular occlusion

A unique difference between APS and cAPS is the finding of microthromboses in patients who died because of fulminant cAPS onset [41]. The involvement of microvessels in cAPS resembles the physiopathological mechanisms depicted in similar conditions such as disseminated intravascular coagulation (DIC). DIC has been described as a widespread intravascular coagulation of fibrin and ultimately thrombotic occlusion of small and midsize vessels [42]. Noteworthy infectious diseases particularly septicaemia are the most common “trigger” of DIC [43]. cAPS and DIC share common precipitating factors (infection, trauma, surgery, obstetric complications and malignancy) [44–46], all of which may induce a generalized inflammatory response, characterized by the activation of cytokine network. The release of several cytokines may cause the impairment function of protein C and additional pathways of the natural anticoagulants. Furthermore a hypofibrinolytic state has also been observed in both DIC and APS [2,43]. Triggers of the activation of diffuse coagulation at the microvessel level in patients with infections are cell-specific membrane components of microorganisms, such as LPS or endotoxin, or bacterial exotoxins (e.g., staphylococcal α hemolysin). All these components may induce a generalized inflammatory response [36]. The release of IL-1, IL-6 and TNF-α by ECs represents a common event triggered by either infection or aPLAs during the development of thromboses in microvessels in cAPS. Based on such findings often seen in similar conditions (DIC and sepsis), it can be suggested that a massive release of cytokines might be responsible for clotting activation at the microvascular organ bed in cAPS [6]. Interestingly, the binding of lupus anticoagulant has been reported to induce apoptosis in umbilical vein ECs, followed by the characteristic microvascular thrombosis described in cAPS [47]. A recent study suggested that apoptotic EC injury is the underlying primary physiopathological mechanism for thrombotic microangiopathies [48], which share also several clinical and pathological features with cAPS.

Table 2
Physiopathological features of cAPS and microangiopathic anemias.

	cAPS	TTP	HIT	DIC
Thrombotic mechanisms	Antibody-mediated thrombosis (acquired)	Antibody-mediated thrombosis or absence of enzyme	Antibodies to PF-4, IL-6, etc. Complexed with heparin	Acute infections with septicaemia, malignancies, drug-induced, cirrhosis, etc.
Antigenic target(s)	Annexin V β2-GPI Prothrombin	Metalloprotease ADAMTS13	Platelet factor-4–heparin (PF-4)	NA
Anatomic site of thrombosis	Microvasculature	Microvasculature	Venous and arterial Microvasculature (unusual)	Microvasculature, venous and arterial
Schistocytes	–/+	++	Rarely	+/-
Platelets and coagulation factors	± Platelet consumption	Platelet consumption	Platelet consumption	Consumption of coagulation factors V, VIII, XIII, I and platelets
Fibrin degradation products	–	–	+	+++
aCL	++	±	–	±
Anti-β2-GPI	+++	±	–	±

cAPS: catastrophic antiphospholipid syndrome; TTP: thrombotic thrombocytopenic purpura; HIT: heparin-induced thrombocytopenia; DIC: disseminated intravascular coagulation; aPLAs: antiphospholipid antibodies; aCL: anticardiolipin antibodies. Adapted from Ref. [51].

7. Microangiopathic anemia and thrombocytopenia in cAPS

The finding of both thrombocytopenia and microangiopathic anemia in cAPS resembles the physiopathological mechanisms described in microangiopathic hemolytic anemias (MHAs) such as thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome, malignant hypertension, and the hemolytic anemia, elevated liver enzymes and low platelet count (HELLP) syndrome [49,50]. MHAs are characterized by thrombocytopenia, fragmentation of erythrocytes, and increased levels of lactate dehydrogenase. The severity of these abnormalities reflects the extent of the microvascular aggregation of platelets. A cardinal sign of MHAs is the presence of fragmented red cells (schistocytes) in the blood smear. Schistocytes are probably produced as blood flows through turbulent areas of the microcirculation that are partially occluded by platelet aggregates. This process causes hemolysis inside microvessels [49]. cAPS shares several features with MHAs. As an example, a common feature among cAPS, TTP and an additional entity, the heparin-induced thrombocytopenia (HIT), is the presence of antibody-mediated thrombosis [51]. Otherwise, another entity, the idiopathic thrombocytopenic purpura (ITP), is also characterized by the presence of autoantibodies reacting with platelet-specific antigens resulting in thrombocytopenia as well [52]. Indeed aPLAs are present in about 30% of cases of idiopathic thrombocytopenic purpura (ITP) and furthermore thrombocytopenia is detected in about 20% of patients with cAPS [6]. Another common feature among MHAs and cAPS is the endothelial damage, which causes the aggregation of platelets, the formation of thrombin, and the impairment of fibrinolysis. Although cAPS and thrombotic microangiopathies share several physiopathological features, they are also distinguishable conditions [53]. In ITP and HIT, antibodies bind to platelets or to complexes on the platelet surface causing either their clearance by the reticuloendothelial system or their destruction by complement-mediated lysis. This phenomenon has not been described in cAPS hitherto. Interestingly, ITP patients with persistent aPLAs may later develop thrombotic complications, particularly when platelet counts normalize after corticoid therapy or splenectomy [38]. A comparison among cAPS and MHAs regarding their physiopathological features is summarized in Table 2.

8. Genetic risk factors for cAPS

It is still unclear why some patients develop thrombosis affecting large vessels (APS), whereas others develop progressive microthromboses and multiorgan failure (cAPS). Those findings suggest that likely cAPS occurs in genetically susceptible individuals in response to a triggering stimulus. Currently, several genetic forms of

thrombophilia are predisposing risk factors for vascular thrombosis. Those include a depression of the natural anticoagulant system (mutation of Factor V Leiden, protein S, protein C, antithrombin III deficiency), endogenous hypofibrinolysis (PAI-1 4G/5G, t-PA I/D, beta-fibrinogen –455G/A gene polymorphisms), prothrombin (Pt) G20210A mutation and hyperhomocysteinemia mostly related to MTHFR C677T mutation [54]. Although the complete spectrum of genetic thrombophilia has not been studied in patients with cAPS, a molecular approach in a case report showed no evidence of an underlying genetic thrombophilic syndrome [55]. By contrast, in another study [45], five women with cAPS were followed up for five years. In 3 patients the triggering event was severe preeclampsia and in two patients infection (pneumonia, septicaemia). A history of obstetric complications was remarkable in all patients. Genetic thrombophilia was found in all women. Heterozygous forms of MTHFR C677T, 675 4G/5G PAI-1, –455G/A beta-fibrinogen gene polymorphisms, homozygous I/D polymorphism of t-PA gene, heterozygous I/D ACE, 807C/T GPIa receptor, 740C/T angiotensinogen gene polymorphisms were identified in different patients. Noteworthy multigenic thrombophilia was found in 3 patients [45]. However currently it is still unclear if patients with cAPS have an increased risk due to a “hidden” genetic thrombophilic background. Additional genetic risk factors have been recently identified in patients with APS concerning the production and reactivity of aPLs. In one study, a single amino-acid change at position 247 (leucine/valine) in β 2-GPI was associated with an increased production of anti- β 2-GPI antibodies [56]. The allele encoding for valine at position 247 in the β 2-GPI was associated with higher and stronger reactivity of anti- β 2-GPI antibodies when compared with the allele encoding for leucine at position 247 in the β 2-GPI. It suggested that the allele encoding for valine at position 247 in β 2-GPI might be a genetic risk factor for developing APS [56]. The genetic susceptibility to develop cAPS regarding those findings has not been assessed yet. However it is tempting to speculate that additional polymorphisms distinct to those described in APS might be associated with particular findings characterizing cAPS itself.

9. Concluding remarks

The physiopathology of cAPS involves several mechanisms which are not well understood. Several reasons have made difficult to study the physiopathology of cAPS. The sporadic distribution of cases, the difficulty of collecting blood and serum samples, the high rate of mortality and the often interpretation of its clinical picture as related conditions constitute the main impediments. However it is clear that a cascade of events is needed before full clinical expression of cAPS (Fig. 1). The activation of endothelial cells is likely to occur by autoantibodies which might constitute the first step in the pathogenesis [13]. cAPS is also characterized by a diffuse thrombotic microvasculopathy involving several organs. Noteworthy an intriguing association between cAPS and infection suggests molecular mechanisms of mimicry, which might lead to the generation of autoantibodies to natural anticoagulants cross-reacting with the components of associated infectious microorganisms [7]. cAPS resembles severe sepsis in its acute presentation, with features of SIRS leading to multiple organ dysfunction. Additional findings such as thrombocytopenia and anemia which are often described in similar conditions are also remarkable features of cAPS, but the mechanisms of their induction remain unclear. Although genetic thrombophilia might be a possible predisposing risk factor for cAPS especially during obstetric complications, currently it is not possible to predict cAPS onset based on the assessment of genetic risk factors. Otherwise there are no randomized controlled trials evaluating the efficiency of any medication, however when cAPS is suspected, aggressive multimodal treatment is required. A combination of anticoagulation plus corticosteroids plus plasma exchange or

intravenous immunoglobulin (IVIG) has the best survival rates [4]. The use of specific IVIG that includes anti-idiotypic antibodies has been studied in animal models of antiphospholipid syndrome [57]. As described above, one of the most important physiopathological steps in cAPS is the activation of ECs. Exposure of ECs to anti-idiotypic β 2-GPI monoclonal antibodies led to the inhibition of ECs activation, as suggested by decreased expression of adhesion molecules [57]. Another strategy is the design of peptides preventing the ECs activation in cAPS as it has been shown in the prevention of induction of experimental APS in mice [58]. Interestingly, synthetic peptides capable of blocking the binding of anti- β 2-GPI antibodies to β 2-GPI in APS have also been reported to share amino-acid sequence homology with the membrane particles of different bacteria and viruses [58]. Those data constitute an additional support to the theory predicting that epitope mimicry is involved in the propagation of autoimmune-mediated thrombosis in APS but might also be suggested to explain the thrombotic phenomena in cAPS [7,59]. The most important future objective is to collect blood and serum samples from patients with cAPS, especially during acute episodes. This will permit laboratory studies on the physiopathology of cAPS, including autoantibodies [60], cytokine profile, and polymorphisms in natural anticoagulants. Base on additional findings studies in animal models will help to understand better this unique and interesting condition.

10. Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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