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Review

The role of infectious diseases in the catastrophic antiphospholipid syndrome

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ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS), also called "Asherson syndrome", is a variant of the antiphospholipid syndrome (APS) that occurs in less than 1% of APS cases. The etiology of CAPS is uncertain; however, several triggering factors have been recognized. The most common of these are infectious diseases, particularly those of the respiratory tract. CAPS pathogenesis is incompletely understood, but several theories have been proposed, such as the molecular mimicry theory, which describes the production of anti-β2-glycoprotein I (GP1) antibody in response to infection. The process is complex and involves the activation of Toll-like receptor 4 (TLR-4), which triggers a cytokine storm, followed by endothelial alterations that induce a procoagulant state.
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Contents

1. Introduction

Antiphospholipid syndrome (APS) is defined as the combination of arterial and venous thrombotic events, or repeated miscarriages with the presence of antiphospholipid antibodies. This syndrome may present in an isolated form or in association with other autoimmune diseases [1].

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Less than 1% of patients develop an accelerated form of APS with multiple organ failure known as catastrophic antiphospholipid syndrome (CAPS) [2–5]. The lack of previous history of APS does not exclude the diagnosis of CAPS [5] since CAPS may be the first manifestation of APS [4].

CAPS is a potentially lethal condition because generalized intravascular thrombosis results in ischemia and multiple organ failure [4], which in contrast to APS, CAPS predominantly affects the microvasculature [3,6]. Thrombotic events occur simultaneously or in a short period of time in multiple locations in CAPS while in APS only great vessels are affected and thrombotic events are sporadic and often confined to one location [3].

2. Historical perspective

In 1987, a case of a patient that developed gangrene in the extremities after thiazide diuretic administration was reported in the Weekly St Thomas Rheumatology Meeting. This patient presented with increased levels of antiphospholipid antibodies (aPL), serological features of disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). In 1990, similar cases were reported, two with Sjögren syndrome and other two with primary APS. Later, Harris described this condition as a "devastating coagulopathy/vasculopathy associated with aPL" [7]. In 1992, Ronald Asherson gathered the information of 10 similar cases with multiple organ failure, including the aforementioned, in which 50% of the cases had a fatal outcome and presented clinical features that differed vastly from those with the "classical" or simple APS [8]. He named this disease CAPS [7,9]. It was then determined that this new syndrome, although uncommon, was life-threatening and carried a poor prognosis [10]. The eponym was proposed for the first time and accepted in the "Biannual Phospholipid Meeting 2002" held in Taormina, Sicily and published a year later in France, and is known since then as "Asherson Syndrome" [3].

An international CAPS registry was created in 2000 to keep track of all published reports, as well as the newly diagnosed cases globally [11]. In 2013, there were 446 documented cases, and of those, only 45 showed clinical manifestations before 18 years old [12], making this condition rather uncommon in children and difficult to diagnose since it can be confused with other diseases more commonly seen in the pediatric population, such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) [1]. Around 72% of patients were women, with a mean age of 37 years (range 11–60) [11].

3. Pathogenesis

In 2000, Asherson and Shoenfeld postulated the hypothesis of "molecular mimicry" [13] to explain the role of infectious diseases in the development of CAPS. According to this hypothesis, aPL and anti-β2-GPI can be produced after the exposure to peptides from bacteria and viruses that resemble β2-GPI [3,14]. There is evidence of a genetic predisposition to produce aPL and anti-β2-GPI. A relationship with HLA class II genes has been described, specifically with HLA-DRB1*04, DRB1*07 (0701), DRB1*1302, DR53, DQB1*0301 (DQ7), *0302 and *0303 polymorphisms. HLA-DPB1 alleles, HLA-DM polymorphisms and β2-GPI valine/leucine 247 polymorphisms are also associated with CAPS [15].

Human β2-GPI, also known as apolipoprotein H, is a membrane-adhesion glycoprotein present in blood plasma at a concentration of around 150 to 300 μg/ml. This glycoprotein consists of 326 amino acid residues [16] which bind to negatively charged phospholipids, lipoproteins, activated platelets, endothelial cells, trophoblasts and monocytes. β2-GPI is considered a natural anticoagulant because of its inhibitory effect on prothrombinase, ADP induced platelet aggregation and the synthesis of platelet factor IX. The production of anti-β2-GPI antibodies induced by the homology between bacterial proteins and the β2-GPI favors a hypercoagulable state, and recent evidence shows that they also activate toll-like receptor 4 (TLR-4) [17].

TLRs are a key component of the innate immune response which recognize specific microbial molecules, including lipopolysaccharides (LPS). The activation of TLR-4 induces the nuclear translocation of NF-κB, resulting in the activation of cytokine gene promoters that induce a massive increase in the production of IL-1, IL-5 IL-6, IFN-γ and TNF-α [3,5]. These events produce a "cytokine storm" which is responsible for the development of the systemic inflammatory response syndrome (SIRS) [15] (Fig. 1).

Other risk factors associated with the development of CAPS include endogenous hypofibrinolysis (PAI-1 4G/5G, t-PA I/D), and G20210A or MTHFR C677T prothrombin mutations. These mutations provoke an increased expression of pro-adhesive and pro-coagulant molecules on the cell surface such as tissue factor [18] which activate inflammatory and coagulation pathways. In 1998, Kitchens presented the theory of "thrombotic storm"; it postulated that while clots continue to generate thrombin [15], coagulation is perpetuated by fibrin production and activation of the coagulation and inflammation cascades by activated protease receptors [5]. Fibrinolysis is decreased when plasminogen activator inhibitor-1 (PAI-1) is increased and when natural procoagulant proteins like C protein, antithrombin and annexin are consumed [15]. Furthermore, in septic states there are plenty of anionic substances that have been found to increase the formation of antibody complexes [5].

Although infections are the main triggering factor, it has been recently suggested that thrombocytopenic states, low levels of vitamin D [15] and high levels of ferritin could induce CAPS [18,15]. Ferritin is an iron-binding protein essential for iron storage and homeostasis. This protein facilitates iron availability for vital cellular processes but also has a protective function on other proteins, lipids, and DNA from the potentially toxic effects of iron [19]. The secretory pathways of serum ferritin are incompletely understood; however, it has been observed that hepatocytes, macrophages and Kupffer cells secrete ferritin. Iron-free ferritin is called apoferritin, while iron-bound ferritin is denominated holoferritin, or just ferritin. Each apoferritin is formed by 24 subunits of two kinds: subunit H and subunit L. Depending on the type of tissue and the physiological status of the cell the ratio of H/L can vary. In the liver and spleen the subunit L predominates, while subunit H is found in higher quantities in the heart and spleen. Ferritin expression is regulated by oxidative stress, thyroid hormones, growth factors, second messengers, hypoxia-ischemia and hyperoxia. In animal models, the administration of LPS can increase ferritin expression. The L-ferritin, (ferritin formed predominantly by de L subunit), can stimulate cell proliferation, independently of iron availability (Table 1).

There is evidence that ferritin levels not only reflect an acute phase response, but rather they have an active role in the inflammation process [20]. Ferritin also acts as a signaling molecule and mediator of immune processes, probably through binding to its T-cell immunoglobulin and mucin domain 2 (TIM-2) receptor, which induce suppression of delayed-type hypersensitivity, anergy, suppression of antibody production by B lymphocytes, decrease in phagocytosis and regulation of granulomonocytopoiesis. Ferritin also negatively regulates cells involved in Th2 immune reaction, influencing immune tolerance and autoimmunity. Ferritin may also be related with thrombosis through the induction of inflammatory molecules such as ICAM1 (intercellular adhesion molecule 1). On the other hand, hyperferritinemia can be induced by proinflammatory cytokines via an increase in ferritin synthesis by macrophages. In addition, high levels of ferritin can contribute to the development of a cytokine storm and the activation of endothelial cells [20].

Moderate to high levels of ferritin in LES, rheumatoid arthritis and multiple sclerosis have been reported, thus it has been proposed as an early marker for APS in patients with LES. A role of ferritin in autoimmune diseases has been suggested by several studies. Elevated anti-ferritin antibodies have been found in patients with a variety of autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, rheumatic polymyalgia and Takayasu arteritis. In a study done by

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