Best Practice & Research Clinical Rheumatology 31 (2017) 334–341

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

4

Mechanisms of thrombosis in systemic lupus erythematosus and antiphospholipid syndrome

Philip G. de Groot*, Bas de Laat

Synapse Research Institute, Maastricht, The Netherlands

Keywords:
β_2-glycoprotein I
Antiphospholipid
Cell activation
Lupus anticoagulant
Complement
Mouse models
Prothrombin
Anionic phospholipids

A B S T R A C T

The presence of antiphospholipid antibodies is one of the most common acquired risk factors for thrombosis. Antiphospholipid antibodies is a collective term for a set of autoantibodies with closely related but different specificity. Experiments in which isolated patient antibodies were injected into mice have shown that a specific subset of autoantibodies, those directed against the first domain of plasma protein β_2-glycoprotein I, can explain the increased risk of thrombosis. Experiments performed with these mice have shown that autoantibodies against β_2-glycoprotein I bind to and activate cells such as endothelial cells, monocytes, and platelets. Activation of these cells, all involved in the regulation of hemostasis, results in a shift towards a prothrombotic state. How this process is regulated, whether this is the only mechanism involved, and whether this is the only subpopulation responsible for the increased thrombotic risk is unknown. In this review, we will critically discuss what is known and what is debatable on the pathophysiology of antiphospholipid syndrome.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects many different organs. Clinical presentation of this syndrome is extremely variable and heterogeneous. The calculated prevalence is about 20–150/100,000, mainly affecting people between 15 and 44 years of age, with a two-fold prevalence for black women. On average, Hispanics and African-Americans are diagnosed with SLE at a younger age and with more severe forms of the disease than Caucasians [1]. SLE itself is an

* Corresponding author. Oxfordlaan 70, 6229 EV Maastricht, The Netherlands.
E-mail address: Ph.degroot@thrombin.com (P.G. de Groot).

https://doi.org/10.1016/j.berh.2017.09.008
1521-6942/

independent risk factor for developing both arterial and venous thrombotic events [2]. The risk of developing a thrombotic event is further increase when associated with the presence of inherited or acquired pro-thrombotic abnormalities. In particular, a striking increase in the number of thrombotic events was observed when SLE was associated with antiphospholipid antibodies (aPL). Cervera et al. [3,4] showed that in a cohort of 1000 SLE patients 9.2% of the patients had a history of thrombosis at inclusion and that 1.8% of the included patients died as a consequence of thrombotic complications. These deaths were always associated with the presence of aPL.

The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of aPL in patients with thrombotic complications or pregnancy morbidity. The syndrome was first described in combination with SLE, but later on it was found that the syndrome is more common in the absence of SLE than in its presence. The presence of aPL has been described in about 40% of SLE patients, while about 20% of APS patients have SLE. The presence of antiphospholipid antibodies in the general population has been estimated up to 5%. However, transient presence of aPL has been associated with infectious diseases and the risk of developing thrombosis after a transient presence of aPL is negligible. The prevalence of APS is much lower than the presence of aPL, about 40–50/100,000 individuals. The incidence of new patients is about 5/100,000 persons every year [3]. It has been shown that patients with SLE and antiphospholipid antibodies (secondary APS) have a higher risk of thrombotic complications than patients with only antiphospholipid antibodies (primary APS). The thrombotic risk in patients with aPL is enhanced by the presence of classic risk factors such as smoking, hypertension, hyperlipidemia, and the use of specific oral contraceptives. APS differs from other hypercoagulabilities because patients with antiphospholipid antibodies can suffer from thrombotic complications in every vascular bed, although deep venous thrombosis (DVT) and pulmonary embolisms account for 60% of the thrombotic complications and stroke accounts for 30% of all the complications. Interestingly, in a cohort of 1000 APS patients, 9.3% of the patients died in a 10 years follow-up, one-third of them of thrombotic complications, indicating that the clinical consequences of having APS is more than thrombosis alone [5].

SLE and thrombosis

The most important biomarker for the risk of thrombosis in patients with SLE is the presence of aPL; however, patients with SLE but without aPL have a two-fold higher risk for thrombosis. It is unclear why SLE is a risk factor independently from aPL. A study by the Karolinska Institute [6] on a cohort of SLE patients showed that 50% of SLE patients died of some form of CVD. Results showed early and accelerated onset of atherosclerosis in SLE patients (40% vs. 6%–10% of a homogeneous sample among controls) [7]. This is associated with the early onset of cardiovascular disease (first event 47–64 years of age), even in pre-menopausal women, thus resulting in a 2- to 10-fold greater risk of developing cardiovascular disease. Among traditional risk factors, only smoking, high soluble vascular cell adhesion molecule-1, high-sensitivity C-reactive protein, anti-β_2 glycoprotein-1, and aPL remained predictive of CVM. Traditional risk factors cannot be fully explained the increased vascular pathology. There are now strong indications that aberrant innate and adaptive immune responses could also contribute to the development of accelerated atherosclerosis in these patients. Defective apoptosis, abnormal lipoprotein function, autoantibodies, aberrant neutrophil responses, and a dysregulated type I interferon pathway all contribute to endothelial dysfunction [8]. SLE macrophages have an inflammatory phenotype that may drive progression of plaque [9].

No disturbances of the hemostatic balance have been described in patients with SLE, so the most obvious conclusion is that vascular disturbances are responsible for the thrombotic risk. However, SLE is a risk factor for both venous thrombosis and arterial thrombosis [1], and vascular damage is considered a primary risk factor for arterial thrombosis. A role of immune complexes and FcγRIIa has been suggested [10,11], but a convincing explanation is not available.

APS and thrombosis

Experimental animal models have shown that antiphospholipid antibodies are indeed the cause of the increased thrombotic risk. Infusion of antiphospholipid antibodies into mice, rats, or hamsters does