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WORD COUNT	1125	TIME SUBMITTED	12-MAR-2024 03:40PM
		PAPER ID	107503227

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 89432
Manuscript Type: EDITORIAL

Protein C deficiency with venous and arterial thromboembolic events

Zhang N *et al*. Protein C deficiency and thromboembolism

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Abstract

Protein C is a key component in the vitamin-K dependent coagulation pathway. It exerts anticoagulant effects by inactivating factors V and VIII. Acquired or inherited protein C deficiency results in a prothrombotic state, with presentations varying from asymptomatic to venous thromboembolism. However, there has been an increasing number of reports linking protein C deficiency to arterial thromboembolic events, such as myocardial infarction and ischemic stroke. This editorial focuses on the association between protein C deficiency and thromboembolism, which may provide some insights for treatment strategy and scientific research.

Key Words: Protein C deficiency; Venous thromboembolism; Myocardial infarction

Zhang N, Sun DK, Tian X, Zheng XY, Liu T. Protein C deficiency with venous and arterial thromboembolic events. *World J Clin Cases* 2024; In press

Core Tip: Protein C deficiency impairs the balance between procoagulant and anticoagulant system which results in predominantly venous thromboembolism. However, there has been an increasing number of reports linking the condition to arterial thromboembolic events. A thorough understanding of protein C deficiency is essential

for the development of new management strategies against protein C deficiency-related thromboembolism events.

INTRODUCTION

In this editorial we comment on the case report by Seo *et al*[1] published in the recent issue of the *World Journal of Clinical Case*. The authors presented a case who had unprovoked pulmonary thromboembolism and deep vein thrombosis 9-month back and now presented with acute myocardial infarction without any underlying major risk factors for atherosclerosis cardiovascular disease, which possesses important clinical implication[1]. Therefore, in this editorial, we discuss the biology of protein C, pathophysiology of protein C, protein C deficiency-related venous and arterial thromboembolism (ATE), as well as treatment strategy.

PROTEIN C AND PROTEIN C DEFICIENCY

Protein C is a vitamin K dependent proenzyme, which is synthesized in hepatocytes and circulates in the blood as an inactive zymogen[2]. Thrombin with thrombomodulin cleaves PC, converting it into its activated form, activated protein C. Along with its co-factor protein S, activated protein C inhibits thrombin generation by inactivating activated factors V (Va) and VIII (VIIIa)[3]. Both factors Va and VIIIa are required for factor X activation, which then converts prothrombin to thrombin. Factors Va and VIIIa act as substrates for APC, which irreversibly inactivates them through proteolytic activity on cleavage sites, thereby inhibiting their pro-coagulant effect (Figure 1)[4]. In addition to the anticoagulant function, APC also exhibits potent cyto-protective and anti-inflammatory, as well as indirect fibrinolytic properties[5].

A deficiency of protein C impairs the balance between procoagulant and anticoagulant system and engenders a prothrombotic state. The etiology of protein C deficiency may be genetic (heterozygous or homozygous) or acquired, the latter often due to vitamin K antagonist therapy or liver disease. Hereditary PC deficiency is caused by mutation in the protein C (PROC) gene located on chromosome 2q14.3[5]. It has been reported that more than 500 mutations identified throughout the PROC gene length may lead to inherited PC deficiency. The molecular basis of inherited protein C deficiency is complicated, results from a recent study has demonstrated that nucleotide variations in

the signal peptide and propeptide of protein C lead to protein C deficiency by differently affecting the biological process of protein C, including posttranscriptional pre-mRNA splicing, translation, and post-translational modification[6]. Heterozygous protein C deficiency is estimated to occur in 0.02%-0.05% of the general population, whereas homozygous protein C deficiency is much rarer which may lead to disseminated intravascular coagulation, thrombosis and purpura fulminans that often appears within hours or days of birth[7]. Most cases of inherited protein C deficiency in clinical practice belong to heterozygous deficiency, with presentations varying from asymptomatic to thromboembolism events.

PROTEIN C DEFICIENCY AND VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) represents the cardinal clinical manifestation of heterozygous protein C deficiency. It has been reported that patients with PC deficiency have a 10- to 15-fold higher risk of VTE than wild-type individuals, and nearly 5% of patients with VTE may have heterozygous protein C deficiency[8,9]. The risk of VTE among patients with PC deficiency varies, which may be related to both the degree of deficiency and the presence of other acquired or inherited risk factors for thrombosis, such as fracture, immobilization, and surgery. Additionally, it has been reported that there is a 38% recurrence rate of VTE among patients with protein C deficiency and prior VTE[10]. Therefore, evaluation of PC deficiency, should be considered in patients with recurrent VTE.

PROTEIN C DEFICIENCY AND ATE

Compared to the established association between protein C deficiency and VTE, the relationship with ATE remain controversial. A previously large family cohort study has observed a 6.9-fold (95%CI: 2.1-22.2) higher risk of ATE among patients with protein C deficiency before 55 years of age[11]. Protein C deficiency was also observed in 12% of reported cases of myocardial infarction with normal coronary arteries[12]. Besides, as seen in the case reported by Seo *et al*[1] most of the evidence linking protein C deficiency to

ATE events stems from case reports[7,13]. However, some studies failed to observe the association between protein C deficiency and ATE[4]. Therefore, to address the knowledge gap, further large-scale studies are still required to investigate the effects of protein C deficiency on ATE and explore the underlying mechanisms.

MANAGEMENT OF PROTEIN C DEFICIENCY

The management of protein C deficiency are mostly based on previously reported cases and experiences. For severe protein C deficiency cases, lifelong protein C replacement therapy may be required[5]. In addition, according to a recent guideline, subcutaneous protein C concentrate with or without vitamin K antagonists may be the most appropriate long-term management for severe congenital protein C deficiency patients, whereas there is little data available on pharmacokinetics and the most appropriate dosing regimen[14]. For the majority of cases, oral anticoagulants remain the mainstay of treatment option. According to the CHEST Guideline and Expert Panel Report, vitamin K antagonists have been the cornerstone of treatment and secondary prophylaxis in patients with hereditary thrombophilia[15]. Some reported cases suggested a possible role of direct oral anticoagulants in thrombophilic patients, which needs further validation[7]. In addition, there is also a lack of treatment strategies for protein C deficiency-related ATE. Hence, more data is required to establish efficacious strategy for the treatment and secondary prophylaxis in patients with protein C deficiency manifesting with thromboembolic events.

CONCLUSION

Protein C deficiency is a risk factor for thrombophilia, with higher risks of VTE. Emerging data has linked protein C deficiency with increased risk of ATE, which requires further validation in large-scale studies. In addition, future studies are needed to establish efficacious treatment strategy for protein C deficiency-related thromboembolic events.

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