



Contrasting Etiology of Thrombophilia in Asians and Caucasians

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Abstract

Background: The primary risk factor for venous thromboembolism in people of Caucasian ethnicity is resistance to the anticoagulant system of activated protein C, caused by the factor V Leiden variant, whereas that in the Japanese population is reduced protein S activity. In Japanese patients, thrombophilia is primarily caused by dysfunction of the activated protein C anticoagulant, which mainly results from abnormal protein S molecules with reduced anticoagulant activity.

Objective: The purpose of this review is to summarize our research on thrombophilic predisposition in Japanese individuals. We developed a reliable quantitative assay system for precise simultaneous determinations of total protein S activity and total protein S antigen level, using a general-purpose automated analyzer, allowing protein S-specific activity (ratio of total protein S activity to total protein S amount ($\mu\text{g/ml}$) level) to be calculated. Using the protein S-specific activity method, we systematically screened for the etiology of thrombophilia in Japanese patients suffering from venous, arterial and small vessel thrombosis. Decreased protein S-specific activity was found with high incidences in Japanese patients who suffered venous thromboembolism.

Patients/Methods: Our newly developed quantitative analysis of protein S anticoagulant activity could contribute to the early detection of prothrombotic traits in Japanese individuals. Total protein S activity analysis considerably improves the accuracy and reproducibility of measurements, as protein S activity can be measured using a chromogenic substrate without the need for separation of the free and bound forms. The quantitative analysis of protein S anticoagulant activity could facilitate the early detection of prothrombotic traits in Japanese individuals.

Conclusions: In Asians populations such as Japanese or Chinese, thrombophilia is primary caused by dysfunction of the activated protein C anticoagulant system, which mainly results from abnormal protein S or protein C molecules with reduced activities of the activated anticoagulant system.

Text

Venous thromboembolism (VTE) consists mainly of deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a potentially life-threatening condition caused by genetic and acquired risk factors [1,2]. The factor V Leiden (rs6025 or *F5* p.R506Q) variant, which causes the activated protein C (APC) resistance, is a major genetic risk factor for VTE in Caucasian populations [1,2]. However, this is not the case for Asians [3-6].

The most significant genetic risk factor for VTE in Japanese or Chinese individuals is the loss of function of anticoagulant factors, such as protein S or protein C [3-6]. In Asian populations, thrombophilia is primarily caused by APC dysfunction resulting from abnormal protein S or protein C molecule with reduced anticoagulant activity [3-6]. The loss of function, however, is relatively uncommon in Caucasian patients with VTE [1,2].

In both cases — APC resistance in Caucasians and APC dysfunction in Asians — the development of a state in which blood clotting activity becomes comparatively stronger than the anticoagulant activity of APC is the potential triggering mechanism for VTE [6]. A high prevalence of genetic variants associated with protein S deficiency, characterized by reduced activity at normal protein levels, has been reported in Japanese patients with VTE [6].

Until our studies were conducted in the last 25 years, the risk factors for thrombosis in Japanese people were unknown. It has since been shown that reduced APC anticoagulation activity is a critical risk factor [4-7]. Most participants had dysfunction of the APC anticoagulation system, mainly due to reduced protein S or protein C activity in Japanese [4-7] or Chinese [3,8] populations. However,

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these APC dysfunctions described above [4-9] have seldomly detected in healthy individuals or VTE patients of Caucasian origin, and *vice versa* for factor V Leiden and prothrombin G20210A in Asians [5,6].

Our newly developed quantitative analysis of the anticoagulant activity of the protein S could contribute to the early detection of prothrombotic traits in Japanese individuals [6-9]. To identify thrombophilic tendencies and constitutions in Japanese, a novel protein S assay has been developed that combines quantitative analysis of the APC cofactor activity of protein S with quantitative analysis of the amount of protein S [6,7]. The total protein S assay has several advantages [6,7]: it measures total protein S activity (i.e., sum of the free and the bound forms of protein S in plasma), which dramatically improves the accuracy and reproducibility of measurements because protein S activity can be measured using a chromogenic substrate without separating the free and bound forms; the amount of total protein S ($\mu\text{g/ml}$) can be determined, and the specific activity of the protein S molecule can be calculated from the total protein S activity and the total amount of protein S. Finally, protein S deficiency can be detected with high sensitivity and specificity by measuring protein S specific activity [6,7].

The total protein S assay is expected to facilitate the prevention, diagnosis and treatment of VTE by enabling the accurate and rapid measurement of reduced protein S activity in an outpatient setting [7]. Acquired risk factors for VTE include surgery, prolonged immobilization, oral contraceptives, hormone replacement therapy, pregnancy, the postpartum period, cancer and advanced age [1,2]. Measurement of protein S specific activity could be useful for detection, diagnosis and selection of personalized treatment not only in patients with VTE, but also in disaster refugees and women with recurrent miscarriages, as well as in healthy individuals who may have developed VTE due to their constitutional background, such as those with reduced protein S specific activity [5,7].

Japan is prone to earthquakes, and disaster survivors forced to live in cars or temporary shelters are at increased risk of developing VTE due to immobilization and dehydration. Following the Chuetsu earthquake in Niigata Prefecture, Japan on October 23, 2004, a 48-year-old woman died suddenly on October 28 of a pulmonary embolism. She had evacuated her home with her family and spent five nights in her car. She died of a pulmonary embolism in the car [10]. After the Great East Japan earthquake on March 11, 2011, many people forced to live in cars or temporary shelters suffered VTE, are similar to the situation after the Chuetsu earthquake.

The genetic and acquired risk factors for VTE have been determined primarily on the basis of patients in Caucasian origin [1,2]. It is important, however, to note that genetic variants have different allele frequencies and risk significance depending on an individual's ethnic background [5-7]. For example, factor V Leiden

[1,2] and protein S Tokushima [5] are two such variants that may have different effects depending on ethnicity. There are also ethnic and regional differences in acquired risk factors [1,2]. As international staff exchanges become more frequent, it is necessary to consider the differences in genetic and acquired risk factors in different populations. The total protein S assay [6,7] could be used to detect thrombotic states due to APC-dysfunction caused by abnormal protein S molecules not only in Asian populations [5-9] but also in other populations including Caucasians. It also provides a rapid and cost-effective approach to identifying carriers of abnormal circulating protein S molecules without the need for genotyping [6,7].

In conclusion, thrombophilia in Japanese or Chinese individuals may be primarily due to "APC-dysfunction" caused by reduced activity of protein S or protein C [5,6]. We have therefore developed a quantitative analysis of protein S activity to identify such a thrombophilic tendency and to screen for thrombophilic constitutions in Japanese individuals. The proposed newly developed assay system for protein S activity [6,7] could contribute to the early detection of thrombophilic traits at least in Japanese individuals.

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