ACTIVATED PROTEIN C RESISTANCE IN BEHCET'S DISEASE

THESIS

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BY

Hoda Abdel Badaee Hussein
M.Sc., Internal Medicine
Cairo University

Supervisors

Prof.
Gaafar Ragab
Professor of Internal Medicine
Faculty of Medicine
Cairo University

Prof.
Maher El Amir
Professor of Internal Medicine
Faculty of Medicine
Fayoum University

Prof
Sherif Nasseh Amin
Professor of Clinical Pathology
Faculty of Medicine
Cairo University

Cairo University - 2010

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Abstract

Background: Behçet's disease (BD) is a chronic systemic disorder of unknown etiology characterized by recurrent oral and/or genital aphthous ulcerations, uveitis and skin lesions. Clinical presentation of this disorder is multifaceted and includes articular, central nervous system, gastrointestinal, renal, urogenital, pulmonary and cardiovascular manifestations, all of which are associated with systemic vasculitis, a pivotal patho-physiological feature of BD. Several studies had investigated the prevalence and role of several factors with procoagulant activity in thromboembolic phenomena in patients with BD. Most studies investigated these factors separately and yielded conflicting results.

objective: The aim of this study was to evaluate the prevalence of activated protein C resistance in Egyptian patients with Behçet's disease. Also, to detect hyperhomocysteinemia in selected cases (with vascular complications) to asses their relationship with thromboembolic complications.

Methods: This study included thirty two patients with Behçet's disease who fulfilled the International Study Group Criteria for diagnosis of Behçet's Disease. Ten normal healthy subjects served as control. Activated protein C resistance test was done by coagulation assay for all patients and the study control. Total plasma homocysteine concentration was measured in ten selected patients from the studied group who had vascular complications.

Result: Our study showed that frequency of activated protein C resistance in the patients (18.8%) was higher than the controls (10%) and it was higher in the group with vascular affection (29%) than those without (6.6%), but without statistical significance. Also, our study detected three patients with vascular complications having hyperhomocysteinemia.

Conclusion:

These results suggested that activated protein C resistance and hyperhomocysteinemia might be a risk factor for the development of thrombosis in Egyptian Behçet's disease patients. Further larger studies will be needed to give strong evidance.

KEY WORDS

Behcetis dhisoaoe_aetivated protein_creistance-homocy steine

Contents

List of abbreviations

APC-R : activated protein C resistance
aPTT : activated partial thromboplastin time
AT : antithrombin
BD : Behcet's disease
BS : Behcet's syndrome
CAP : College of American Pathologists
CBS : cystathionine β-synthase
CD : cluster of differentiation
CNS : central nervous system
CRP : C reactive protein
CT : computerized tomography
DNA : deoxyribonucleic acid
DVT : deep venous thrombosis
ECG : electrocardiogram
EEG : electroencephalogram
ESR : erythrocyte sedimentation rate
EULAR : European League Against Rheumatism
FMF : familial Mediterranean fever
FVL : factor V Leiden
GIT : gastrointestinal tract
HCY : homocysteine
HLA : human leukocytic antigen
HSV : herpes simplex virus
IFN : interferon
IL : interleukin
INR : international normalized ratio
IVC : inferior vena cava
MI : myocardial infarction
MRI : magnetic resonance image
MTHFR : methylenetetrahydrofolate reductase
PC : protein C

PCR : polymerase chain reaction

PS : protein S

PV : probability value

RCT : randomized control trial

SD : standard deviation

SLE : systemic lupus erythematosus

SVC : superior vena cava

TGF : transforming growth factor

TNF : tumor necrosis factor

VEGF : vascular endothelial growth factor

VTE : venous thrombo-embolism

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INTRODUCTION

AND

AIM OF THE WORK

INTRODUCTION

Behçet's disease is a chronic, complex multi-system disease characterized clinically by oral aphthae, genital aphthae, cutaneous lesions, and ophthalmic, neurological, or rheumatologic manifestations. The first description of Behçet's disease was probably by Hippocrates in the fifth century BC, and the first modern account was presented in 1937 by the Turkish dermatologist Hulusi Behçet, who reported on a patient with recurrent oral and genital aphthae and uveitis **(Louden and Jorizzo, 2008).**

Recently, BD was classified into a group of auto-inflammatory disorders, sharing some common innate immune and genetic mechanisms of dysregulation of inflammation, which can cause endothelial damage, activation of coagulation and thrombosis, and underlie vascular morbidity and mortality **(Yazici et al, 2007)**.

The frequency of vascular involvement in Behçet disease ranges from 5% to 30% and develops within 10 years after the initial diagnosis. Vascular involvement can be divided into three subsets: venous occlusion, arterial occlusion, and arterial aneurysm formation. Venous occlusion is the most common manifestation, followed by arterial aneurysm and arterial occlusion **(Chae et al, 2008).**

The pathogenesis of arterial and venous thrombosis in Behçet's disease is not completely understood. It is generally accepted that vasculitis, a hallmark of Behçet's disease, partially explains the initiation of thrombosis in small as well as large blood vessels. Attempts to identify additional prothrombotic factors have so far been conflicting **(Leiba et al, 2004)**.

The great majority of subjects with activated protein C resistance have a genetic mutation in factor V (factor V Leiden). In a multiple series of studies on the prevalence of these mutations among BD patients and possible association with disease activity, ocular involvement, thrombosis, homocysteinemia, CRP and other mutations related to coagulation, the obtained results were controversial **(La Regina et al, 2010)**.

Some studies have shown that hyperhomocysteinemia might be assumed to be an independent and correctable risk factor for thrombosis in BD. Moreover, the association between homocysteine levels and endothelial dysfunction has been shown in patients with BD **(Sarican et al, 2007; Ozkan et al, 2007)**.

AIM OF THE WORK

The aim of this study is to evaluate the prevalence of activated protein C resistance in Egyptian patients with Behçet's disease. Also, to detect hyperhomocysteinemia in selected cases (with vascular complications) to asses their relationship with thromboembolic complications as a pathogenic role. Also, the evidence of coagulopathy in Behçet's disease will direct the need for anticoagulation.

REVIEW OF LITERATURE

CHAPTER 1

BEHÇET'S DISEASE

Background

Behçet's disease is a chronic disease with multisystem involvement characterized clinically by oral and genital aphthae, cutaneous lesions, and ophthalmologic, neurological, and/or gastrointestinal manifestations. The first description of Behçet's disease was probably by Hippocrates in the fifth century BC, and the first modern account was presented in 1937 by the Turkish dermatologist Hulusi Behcet, who reported on patients with recurrent oral and genital aphthae and uveitis and named this group of symptoms as "triple symptom complex". Since Behçet's introduction many musculoskeletal, gastrointestinal, urogenital, cardiac, cutaneous, and neurological symptoms were added and Behçet's disease is designated to a discrete clinical entity **(Louden and Jorizzo 2008).**

In Greece, the disease is named Adamantiades – Behçet's syndrome because Adamantiades presented a case of recurrent hypopyon iritis, phlebitis, oral and genital ulcerations and knee arthritis six years before Behçet's paper **(Adamantiades, 1930)**.

Behçet's disease is a systemic vasculitis of unknown etiology that is found in small and large vessels and characterized by variable clinical features. Almost all patients have recurrent oral ulcers, followed in frequency by genital ulcers, a variety of skin lesions, arthritis, panuveitis, thrombophlebitis, gastrointestinal disease and central nervous system involvement **(Yazici et al, 1998).**

Behçet's disease is an inflammatory disorder of unknown cause, characterized by recurrent oral aphthus ulcers, genital ulcers, uveitis and skin lesion Involvement of the gastrointestinal tract, central nervous system, and large vessels is less frequent, although it can be life threatening. Susceptibility to Behçet's disease is strongly associated with the presence of HLA-B51 allele. Environmental factors such as infectious agents have also been implicated in its pathogenesis **(Sakane et al, 1999)**.

EPIDEMIOLOGY

Prevalence:

Behçet's disease is seen worldwide, with the highest prevalence reported in Turkey (80 to 370 patients per 100,000 inhabitants) and Japan (13.6 per 100,000). Other regions with high prevalence include the Middle East and the Mediterranean (i.e., the “Silk Route”). It is relatively uncommon in northern Europe and the United States (0.1 to 7.5 patients per 100,000 inhabitants) **(Louden and Jorizzo, 2008).**

Cases of Behçet's disease cluster along the ancient Silk Road, which extends from eastern Asia to the Mediterranean basin. Turkey has the highest prevalence: 80 to 370 cases per 100,000 populations **(Kastner, 1997)**. The prevalence in Japan, Korea, China, Iran, and Saudi Arabia ranges from 5 to 20 cases per 100,000 populations **(Kaklamani VG et al, 1998)**. It is lower in western countries. 0.64 per 100.000 in the United Kingdom and 0.12 to 0.33 per 100.000 in the United States **(Zouboulis et al, 1997)**. In Alexandria-Egypt, the prevalence is 7.6 patients per 100.000 populations **(Zouboulis, 1999).**

The disease is very rare among southern Chinese, with only 37 cases identified in the past 20 years in four large regional hospitals in Hong Kong that serve a population of almost 1.5 million people. It has benign course, milder eye manifestations with less common neurological and vascular lesions compared to Japanese, European, and Middle East series (**Mok et al, 2002).**

Some clinical differences were noted between patients with different ethnic backgrounds. There were significantly more female patients in the non-ethnic groups and gastrointestinal disease was significantly more among these patients also. Eye disease prevalence for both groups was less than reported from other centers and may be less severe as none of the patients was blind. These findings may have implications regarding the pathogenesis and the effect of nature on disease presentation in different geographical areas **(Yazici et al, 2009)**.

Age:

The onset of Behçet's disease is typically in young adults, with most cases diagnosed between the age of 15 and 45 years **(Kastner, 1997).** The disease usually occurs around the 3rd decade of life. That is independent of the origin of the patients or their gender. Cases with early and late onset of the disease have also been reported **(Zouboulis,**