PLASMA ANGIOPOIETIN-1 LEVELS IN BEHCET DISEASE: ASSOCIATION WITH THE CLINICAL AND LABORATORY PARAMETERS

Thesis

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ABSTRACT

Objective

Behcet's Disease (BD) is a chronic multisystem inflammatory disorder of unclear etiology. Vascular inflammation, endothelial dysfunction and angiogenesis may be in part responsible for the pathogenesis of BD. The aim of the present study was to assess Angiopoietin-1 (Ang-1) concentrations as a recent angiogenic mediator in plasma of BD patients and to analyze its association with disease clinical features, laboratory parameters as well as disease activity.

Patients and Methods

The present study included 47 BD patients fulfilling the International Study Group criteria for the diagnosis of BD and 30 age and gender matched healthy controls. Demographic, clinical and serological data were prospectively assessed. Activity and severity of BD were also assessed. Plasma Ang-1 levels were measured using enzyme-linked immunosorbent assay (ELISA).

Results

The mean plasma level of Ang-1 in BD patients was significantly lower than healthy controls ($p=0.005$). Mean plasma Ang-1 level in patients with vascular affection was significantly lower than those without vascular affection ($p=0.045$). The mean plasma Ang-1 level was significantly higher in patients with CNS than

those without (p=0.040). There was no significant association between plasma Ang-1 levels and other clinical manifestations nor disease activity or severity. Patients who received cyclophosphamide showed a significant increase in plasma Ang-1 level than those who didn't receive it (p=0.049).

Conclusion

Plasma Ang-1 levels were diminished in our BD patients especially in patients with vascular involvement. Larger studies with further investigations of the precise role of Ang-1 in the pathogenesis of BD are needed and might lead to novel therapies for the clinical management of BD.

Key words Angiogenesis; Angiopoietin; Behcet's disease**;** Vasculitis

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ABBREVIATIONS

ABI	Ankle-Brachial Index
ABIN-2	A20 binding inhibitor of NFkB
ACL	Anticardiolipin
AECA	Anti-Endothelial Cell Antibodies
aFGF	acidic Fibroblast Growth Factors
AICD	Activation Induced Cell Death
ALT	Alanine transaminase
ANA	Antinuclear Antibody
ANCA	Anti-Cytoplasm Antibodies of Neutrophils
Ang	Angiopoietin
anti-dsDNA	anti double stranded DNA
ARDS	Acute Respiratory Distress Syndrome
ASCA	Anti-Saccharomyces Cerevisiae Antibodies
AST	Aspartate trasaminase.
BAL	Bronchoalveolar lavage
BD	Behcet disease
bFGF	basic Fibroblast Growth Factors
C	Complement
CABG	Coronary Artery Bypass Grafting
cANCA	Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies
CD	Cluster of Diffrentiation
CLI	Critical Limb Ischemia

CMV	Cytomegalo Virus
COX	Cyclooxygenase
CRP	C-reactive protein
CSA	Cyclosporine A
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTAP-III	Connective Tissue Activating Protein-III
CTLA–4	Cytotoxic T lymphocyte Antigen 4
CXC, CC, CXC3	Chemokine Receptors
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DNA	Deoxyribonucleic acid
Dok	Downstream of tyrosine kinases.
EBV	Epstein Barr Virus
EC	Endothelial cells
EGF	Epidermal Growth Factor
ELISA	Enzyme-Linked Immunosorbent Assay
ENA-78	Epithelial Neutrophil Activating protein-78
ENG	Endoglin
ESR	Erythrocyte Sedimentation Rate in the first hour
ET-1	Endothelin 1
EULAR	European League Against Rheumatism
FGF	Fibroblast Growth Factor
FK506	Fujimycin (Tacrolimus)
FMF	Familial Mediterranean Fever
Fox	Forkhead box

G20210A	Prothrombin 20210 gene mutation
GC	Glucocorticoids
G-CSF	Granulocyte Colony-Stimulating Factor
GIT	Gastrointestinal tract
GMCSF	Granulocyte-Macrophage Colony-Stimulating Factor
Groα	Growth related oncogene α
GWAS	Genomewide association study
Hb	Hemoglobin
HGF	Hepatocyte Growth Factor
HIF-1, HIF-2	Hypoxia Inducible Factors 1 and 2
HLA	Human leukocyte antigen
HSP	Heat-Shock Proteins
HSV1	Herpes Simplex Virus 1
HUVECs	Human Umbilical Vein Endothelial Cells
IC	Intermittent Claudication
ICAM-2	Intercellular Adhesion Molecule-2
IgA	Immunoglobulin A
IGF-I	Insulin-like Growth Factor-I
IgG	Immumoglobulin G
IgM	Immunoglobulin M
IkB	Inhibitor of NFkB
IL	Interleukin
INFγ	Gamma Interferon
IP-10	Interferon-γ-inducible Protein 10

IRF	Interferon Regulatory Factor 1
ISG	International Study Group
IUGR	Intrauterine Growth Retardation
JAM	Junctional Cell Adhesion Molecules
KD	Kawasaki Disease
KGF	Keratinocyte Growth Factor
MCP-1	Monocyte Chemattractant Protein 1
MDNCF	Monocyte-Derived Neutrophil Chemotactic Factor
MEFV gene	Mediterranean fever gene
MHC	Major histocomptability complex
MIC-A, MIC-B	MHC class I chain-related genes
MIF	Macrophage migration Inhibitory Factor
Mig	Monokine Induced by interferon-gamma
MMP-2	Matrix metalloproteinase-2
MMPs	Matrix Metalloproteinases
MODS	Multiple Organ Dysfunction Syndrome
MRI	Magnetic Resonance Imaging
mRNA	Messanger Ribonucleic Acid
MSCs	Mesenchymal Stem Cells
MTHFR	Methylenetetrahydrofolate reductase
MTX	Methotrexate
MUC 18, Lewis/H	Adhesion molecules
NBD	Neuro Behcet Disease
NO	Nitric Oxide

PAD	Peripheral Arterial Disease
PAF	Platelet Activating Factor
PAFR	Platelet Activating Factor Receptor
PBMCs	Peripheral Blood Mononuclear Cells
PDGF	Platelet-Derived Growth Factor
PECAM-1	Platelet Endothelial Cell Adhesion Molecule-1
PF4	Platelet Factor 4
PGC-1α	Peroxisome-proliferator coactivator 1α pathway
PI3K	phosphoinositide-3 kinase
PMA	Phorbol12-Myristate-13-Acetate
PPAR	peroxisome-proliferator activated receptor
PTX3	Pentraxin-3
RA	Rheumatoid Arthritis
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
RTKs	Receptor for tyrosine kinases
S sangius	Streptococcus sanguis
SAA	Serum Amyloid A
SD	Standard Deviation
SDF-1	Stromal Cell Derived factor-1
sEng	Soluble Endoglin
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index

SNP	Single Nucleotide Polymorphism
SS	Systemic Sclerosis
TGFβ	Transforming Growth Factor β
Th	T helper cells
TIMP	Tissue Inhibitors of metalloproteinases
TLR	Toll Like Receptor
TNFRSF1A	Tumor Necrosis Factor Receptor Gene
TNFα	Tumor Necrosis Factor α
TPA	Tissue Plasminogen Activator
Tregs	T Regulatory cells
TSP-1	Thrombospondin-1
VCAM-1	Vascular Cell Adhesion Molecule-1
VEGF	Vascular Endothelial Growth Factor
VZV	Varicella Zoster Virus
WBC´s	White Blood Cells
WG	Wegner Granulomatosis
WPB	Weibel-Palade Body
αVβ3	Adhesion receptor αVβ3
γδ Tc	Gamma Delta T cells

INTRODUCTION

Behcet's disease (BD) is a systemic vasculitis disorder of unknown etiology, characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions and ocular lesions.

The cause of BD is unknown. It is believed to be due to an autoimmune process triggered by an infectious or environmental agent (possibly local to a geographic region) in a genetically predisposed individual. Interaction of primed neutrophils with endothelial cells is considered a crucial event in the pathogenesis of severe endothelial lesions in BD vasculitis (***Mendes et al., 2009).***

In this regard, the interaction between neutrophils and endothelial cells has been the subject of much study. Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) are antagonistic ligands that bind to the extracellular domain of the Tie-2 receptor, which is almost exclusively expressed by endothelial cells ***(Fiedler et al., 2003)***. The Ang-Tie ligand–receptor system was identified as the second class of vascular-specific receptor tyrosine kinases (RTKs). Angiopoietins and Tie-2 receptor control angiogenic remodeling in a context-dependent manner. Tie signaling is involved in multiple steps of the angiogenic remodeling process during development, including destabilization of existing vessels, endothelial cell migration, tube formation and the subsequent stabilization of newly formed tubes by mesenchymal cells. Beyond this critical role in blood vessel

development, recent studies suggest a wider role for angiopoietins in lymphangiogenesis and the development of the hematopoietic system, as well as a possible role in the regulation of certain non-endothelial cells. ***(Eklund and olsen, 2006).***

In line with these data, significantly elevated Ang-2 concentrations and decreased Ang-1 concentrations has been detected in patients with Systemic lupus erythematosus (SLE) with active disease ***(Kumpers et al., 2009).*** Circulating Ang-2 has been elevated and closely correlates with disease activity and circulating endothelial cells numbers in ANCA associated vasculitis with renal involvement ***(Kumpers b et al., 2009).*** Recently, a preliminary study reported elevated Ang-1 in Korean BD Patients ***(Choe et al., 2010***). But with this exception, no information is available on the role of Ang/Tie system in BD patients.