Study of Chemokine Receptor CCR5 Polymorphism in Rheumatoid Arthritis Patients

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Abstract

The study included 35 rheumatoid arthritis patients (32 females and 3 males) .Patients were diagnosed according to the revised criteria of the American Rheumatism association. They were attending the rheumatology outpatient clinics of Kasr Alaini school of medicine.

All of them had a regular detailed follow up files. Twenty sex and age matched healthy individuals which were also included in the study as a control group.

All patients were subjected to **:** Careful history taking, Disease activity score index (DAS28) ,x-ray staging using Larsen-Dale method, Laboratory investigations in the form of complete blood count, erythrocyte sedimentation rate, rheumatoid factor and CCR5 genotyping by polymerase chain reaction

Key Words :

Antibody - Acquired immune deficiency syndrome - Rheumatoid Arthritis Patients .

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To All Those I say: جزاكم الله خيراً

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List of abbreviations

Ab: Antibody

Ag: Antigen

ACR: American college of rheumatology

AIDS: Acquired immune deficiency syndrome

BCA: B-cell Attracting Chemokine

Bp: Base pair

CCP: Cyclic citrullinated peptide

CD: Cluster of differentiation

CNS: Central nervous system

CRP: C-reactive protein

CSF: Colony stimulating factor

CT: Computed tomography

DAG: diacyl-glycerol

DARC: Duffy antigen receptor for chemokine

DCs: Dendritic cells

DMARD: Disease modifying anti rheumatic drugs

ECM: Extracellular matrix

ENA: Epithelial-cell-derived Neutrophil-Activating protein

ESR: Erythrocyte sedimentation rate

FC: Fragment Crystallized

GC: Germinal center

GCP: Granulocyte Chemotactic Peptide

GDP: Guanosine diphosphate

GPCR: G protein coupled receptor

GRO: Growth-Related Oncogene

GTP: Guanosine triphosphate.

HEVS: High endothelial venules

HIV: Human immune-deficiency virus

HLA: Human leucocytic antigen

INF: Interferon

Ig: Immunoglobulin

IL: Interleukin

IP: Inter-phalangeal

KDA: Kilo dalton

KSHV: Kaposi's sarcoma herpes virus

MCP: Monocyte Chemoattractant Protein

MIG: Monokine induced by Interferon-Gamma

MIP: Macrophage Inflammatory Protein

MRI: Magnetic resonance image

MS: Multiple sclerosis

MTP: Metacarpo-phalangeal

MTX: Methotrexate

NAP: Neutrophil-Activating Protein

NK: Natural killer

NSAID: Non steroidal anti inflammatory

PAD: Peptidyl arginine deiminase

PCR: Polymerase chain reaction

PIP_2: phosphatidylinositol, 4,5 bisphosphate

PIP_3: phosphatidylinositol 1,4,5-triphosphate

PKC: protein kinase C

PLC: phospholipase C

R.A: Rheumatoid arthritis

RANTES: Regulated upon Activation, Normal T-cell Expressed and Secreted

RF: Rheumatoid factor

SDF: Stromal-Derived Factor

SLE: Systemic lupus erythematosus

TARC: Thymus- and Activation-Regulated Chemokine

TGF: Transforming growth factor

Th cells: T helper cells

TIL: Tumor-Infiltrating Lymphocytes.

TNF: Tumor necrosis factor

INTRODUCTION

Rheumatoid arthritis is a systemic chronic inflammatory disease of the joints characterized by the infiltration of the synovial membrane with T lymphocytes and macrophages, and pannus formation over the underlying cartilage and bone **(Zapico et al., 2000).**

The etiology of R.A is unknown, but the development of the disease appears to be the result of a complex combination of environmental, hormonal, and genetic factors. Population and twin studies have shown that multiple genes may be implicated in disease susceptibility (**Gerard et al., 2001)**

The inflammatory process observed in R.A is mediated by chemotactic factors released by the inflamed tissues. Chemokines display a potent chemotactic factors for cells of the immune system, play an important role in both the destructive and the fibrovasculoproliferative phases of R.A. **(Pokorny et al., 2005)**.

The chemokine receptor 5 (CCR5) mediates chemotaxis by the CC-chemokine RANTES, MIP-1α and MIP-1β. This receptor is expressed by lymphocytes exhibiting the TH1 phenotype and by monocytes-macrophages **(Pardis et al., 2005).**

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lymphocytes exhibiting the TH1 phenotype and by monocytes-macrophages **(Pardis et al., 2005).**

CCR5 is strongly expressed on T-lymphocytes from the synovial fluid of R.A patients. Thus, it might be possible that CCR5 is involved in recruitment of inflammatory cells into the inflamed tissue, and any mechanism modulating the CCR5 expression could have an effect in the development of R.A. In this way, a reduced expression of this receptor on lymphocytes and macrophages could attenuate the severity of the disease **(Parahald et al., 2006).**

A 32 base pair (bp) deletion in the CCR5 gene(CCR5 d32)results in a frame shift and premature termination in the region encoding the second extracellular loop of the CCR5 receptor ,producing a non-functional receptor associated with resistance to activation by specific chemokines, and also with reduced in vitro susceptibility to HIV-1 infection. Previous studies have suggested an influence of (CCR5 d32) on R.A **(Pokorny et al., 2005)**.

AIM OF THE WORK

The aim of the present work is to study whether the CCR5 d32 mutation has a negative association with the susceptibility to rheumatoid arthritis and the effect of CCR5-d32allele on the severity of the disease will be also assessed.

Rheumatoid Arthritis

Definition

Rheumatoid arthritis is a chronic systemic inflammatory disorder of unknown etiology that is characterized by its pattern of diarthroidal joint involvement **(West et al., 2002).**

Its primary site of pathology is the synovium of the joints. The synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage and ligaments and leads to damage and deformities **(West et al., 2002).**

Epidemiology and incidence

Rheumatoid arthritis has a worldwide distribution and affects all ethnic groups. The prevalence of R.A. is about 0.5-1% of world population **(smolen & Steiner, 2003).** The prevalence is about 2.5 times higher in women than in men **(Ollier and Winchester, 1999).**

The disease can occur at any age, but the peak incidence is between fourth and sixth decades **(Arnett et al., 1988).** The onset of R.A. appears to be more in the winter than in the summer months **(Gordon and Hastings, 2000).**

Etiology and risk factors

Despite extensive research, the cause of R.A. is unknown. It is thought to be multi-factorial with a combination of many factors that contribute to

the initiation of R.A such as genetic, environmental, autoimmunity, infective factors and endocrinal factors **(McGregor et al., 2000).**

Genetic factors

Multiple genetic determinants appear to contribute to the risk of developing R.A such as: the relative risk in monozygotic twins is 12-26 folds higher than in unrelated individuals, whereas, in dizygotic twins or siblings sharing only 50% of their genes, the risk is only 2-17 folds higher, so this significant difference indicates a genetic basis for the development of R.A **(McGregor et al., 2000).**

R.A. is strongly associated with HLA-DR4 and, to a lesser extent HLA-DR1 and DR-14 positivity with the susceptibility gene or "shared epitope" postulated on the third hyper variable region of HLA-DRB1 **(firestein,2001).** HLA-DR4 occurred in 70% of R.A. patients, compared to about 30% of controls, giving a relative risk of having R.A in those with HLA-DR4 of approximately 4 to 5 folds **(Nepam et al., 1989).**

It has been estimated that genetic factors account for approximately 15% and non-genetic factors for approximately 85% of rheumatoid arthritis **(Weyand et al., 2000).**

Autoimmunity

The identification and characterization of Rheumatoid Factor as a self antibody, was the first evidence that autoimmunity might play a role in R.A. Rheumatoid Factor is a series of antibodies that recognize the Fc portion of