Relation Between Epstein-Barr Virus Infection and Multiple Sclerosis

Thesis

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in **Clinical and Chemical Pathology**

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Ahmed Essam Ali Hussein

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List of Abbreviations

Abb.	Full term
ACE	*Angiotensin converting enzyme*
AIDS	*Acquired immunodeficiency syndrome*
Alb	*Albumin*
ANA	*Antinuclear antibody*
ANOVA	*Analysis of variance*
APCs	*Antigen presenting cells*
BBB	*Blood brain barrier*
Breg	*Regulatory B cell*
CCP	*Cyclic citrullinated protein*
CD	*Cluster of differentiation*
cDC	*Conventional dendritic cell*
CIS	*Clinically isolated syndrome*
CMV	*Cytomegalovirus*
CNS	*Central nervous system*
CR	*Complement receptor*
CRP	*C-reactive protein*
CSF	*Cerebrospinal fluid*
DNA	*Deoxyribonucleic acid*
DNApol	*DNA polymerase*
ds-DNA	*Double stranded DNA*
EA	*Early antigen*
EBERs	*Epstein Barr encoded RNAs*
EBNA	*Epstein Barr nuclear antigen*
EBV	*Epstein Barr virus*
ECG	*Echocardiogram*
EDSS	*Expanded disability status scale*
EIA	*Enzyme immunoassay*
ELISA	*Enzyme linked immunosorbent assay*

List of Abbreviations cont...

Abb.	Full term
EMG	*Electromyocardiogram*
ENA	*Extractable nuclear antigen*
GFR	*Glomerular filtration rate*
GM-CSF	*Granulocyte monocyte colony stimulating factor*
gp	*Glycoprotein*
HbsAg	*Hepatitis B surface antigen*
HCV	*Hepatitis C virus*
HHV4	*Human herpes virus 4*
HIV	*Human immunodeficiency virus*
HLA	*Human leucocyte antigen*
HS	*Highly significant*
HSV	*Herpes simplex virus*
IEF	*Isoelectric focusing*
IFN α	*Interferon alpha*
IFN β	*Interferon beta*
IFN γ	*Interferon gamma*
IgA	*Immunoglobulin alpha*
IgG	*Immunoglobulin gamma*
IgM	*Immunoglobulin mu*
IL	*Interleukin*
IM	*Infectious mononucleosis*
LCL	*Latent cell line*
LMP	*Latent membrane protein*
MBP	*Myelin basic protein*
MHC	*Major histocompatibility complex*
moDC	*Monocyte derived dendritic cell*
MOG	*Myelin oligodendrocyte glycoprotein*

List of Abbreviations cont...

Abb.	Full term
MRA	*Magnetic resonance angiography*
MRI	*Magnetic resonance imaging*
MS	*Multiple sclerosis*
MV	*Mean value*
Nf-L	*Neurofilament light chain*
NK	*Natural killer*
NS	*Not significant*
OCB	*Oligoclonal band*
p value	*Probability value*
PAMPs	*Pathogen associated molecular patterns*
PC	*Personal computer*
pDC	*Plasmacytoid dendritic cell*
PD-L1	*Programmed death ligand 1*
PET	*Photon emission tomography*
PPD	*Purified protein derivative*
PPMS	*Primary progressive multiple sclerosis*
PTLD	*Posttransplant lymphoproliferative disorder*
RBCs	*Red blood cells*
RIG-1	*Receptor retinoic acid inducible gene*
RNA	*Ribonucleic acid*
RNS	*Reactive nitrogen species*
ROS	*Reactive oxygen species*
RRMS	*Relapsing remitting multiple sclerosis*
S	*Significant*
SD	*Standard deviation*
SES	*Socioeconomic status*
SLE	*Systemic lupus erythematosus*
SNPs	*Single nucleotide polymorphism*

List of Abbreviations cont...

Abb.	Full term
SPMS	*Secondary progressive multiple sclerosis*
STD	*Standard*
TCR	*T cell receptor*
Teff	*Effector T cell*
TGF- β	*Transforming growth factor beta*
Th	*T helper*
TLR	*Toll like receptor*
TNF α	*Tumor necrosis factor alpha*
Tr1	*Type 1 regulatory T cell*
Treg	*Regulatory T cell*
UV	*Ultraviolet*
VCA	*Viral capsid antigen*
VDRL-RPR	*Venereal disease research laboratory-Rapid plasma reagin*

INTRODUCTION

Multiple sclerosis (MS) is an immune mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. As true to most autoimmune diseases, it affects females more than males ***(Kamińska et al., 2017).***

Multiple sclerosis can affect the sensory, motor, cognitive, and even autonomic functions of the CNS, leading to a wide range of possible presentations. It takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain especially as the disease advances ***(Lublin et al., 2014)***.

The etiology and pathogenesis of MS is complex and multifactorial, involving many interlacing mechanisms: genetic factors, environmental agents, and autoimmune responses. The environmental factors may include smoking, vitamin D deficiency, lack of sunlight exposure, and infectious agents. Many theories had considered viral infections as a possible cause of MS, in support of which is the presence of clear examples of inflammatory demyelinating disease caused directly or indirectly by viral infections in both humans and animals. In addition, there is a beneficial role of interferon beta

(IFNβ) in MS treatment which is one of the most popular antiviral agents ***(Abdulrahman et al., 2014).***

Epstein-Barr virus (EBV), a herpes virus belonging to the family herpesviridae, is well known for its ability to induce lifelong latent infection. Many diseases are associated with EBV infection, for example, infectious mononucleosis (IM) and many types of malignancies, and it is thought to be related to some diseases of autoimmune origin ***(Chiu and Sugden, 2016)***.

There is obvious similarity between EBV and MS regarding their epidemiological pictures, and it was observed that most MS patients had a history of IM a few years before onset. The relation between EBV and MS may give hope for development of biomarkers for prediction of disease development, early diagnosis, prediction of prognosis, curing or even preventing MS through an anti EBV vaccine or antiviral therapies ***(Toepfner et al., 2012)***.

Aim of the Work

This study aims to analyze the association between EBV infection and MS.

Chapter 1:

Multiple Sclerosis

1. Epidemiology:

Multiple sclerosis is the most common demyelinating disease seen in high income countries. It affects about 2.5 million persons in the world, and has a heterogeneous prevalence worldwide: it is highest in North America (140/100,000 population) and Europe (108/100,000), and lowest in East Asia (2.2/100,000 population) and subSaharan Africa (2.1/100,000) **(Figure 1)**. In several countries, the gender ratio for MS incidence (women/men) went from 2/1 to 3/1 from the 1950s to the 2000s ***(Leray et al., 2016).***

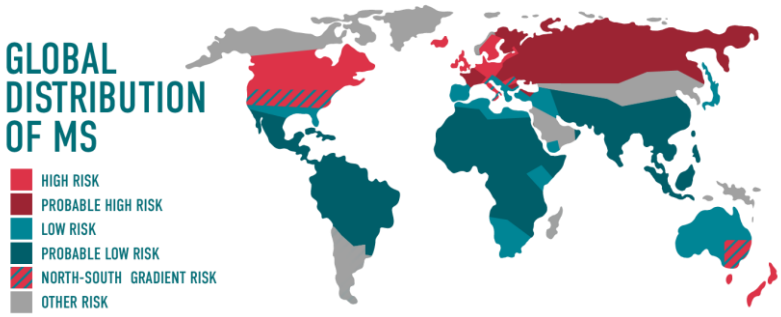

Figure 1: Global distribution of MS ***(Wallin et al., 2019).***

2. Risk factors:

Multiple Sclerosis is believed to occur as a result of some combination of genetic and environmental factors such as infectious agents ***(Kamińska et al., 2017).***

2.1 Genetic factors:

Multiple sclerosis is known to be a partially heritable autoimmune disease. The risk of developing MS increases from typically 1 in 1,000 in the normal population to 1 in 4 for identical twins when one twin is affected. Much of this heritability is now explained and is due almost entirely to genes affecting the immune response ***(Parnell and Booth, 2017).***

Over 200 genetic risk variants, all single nucleotide polymorphisms (SNPs), have now been described and, of these, 110 non-major histocompatibility complex (MHC) genetic loci have been detailed ***(Beecham et al., 2013)*** and 13 MHC loci identified ***(Moutsianas et al., 2015).***

The largest and first identified genetic risk factor is an allele from the MHC class II human leucocyte antigen (HLA)-DRB1 gene, HLA-DRB1*15:01, which increases risk about threefold. The HLA-DRB1 gene is expressed in antigen presenting cells (APCs), and its protein functions in presenting particular types of antigen to cluster of differentiation (CD)4^+ T cells ***(Parnell and Booth, 2017).***

Several MHC class I alleles have also been identified, all with protective effects. These alleles present antigens to $CD8^+$ T cells, or interact with natural killer (NK) cells. $CD8^+$ T cells responding to antigens presented by these protective alleles may be more effectively activated. Or, these alleles could facilitate superior