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Role of Neutrophil/Lymphocyte Ratio as an Indicator of Relapse in Multiple Sclerosis

Thesis

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Presented by

Asmaa Mostafa Eissa

M.B.B.Ch.

Under supervision of

Prof. Dr. Nahed Salah Eldin Ahmed

Professor of Neurology

Faculty of Medicine – Ain Shams University

Prof. Dr. Eman Mahmoud Awad

Professor of Neurology

Faculty of Medicine – Ain Shams University

Dr. Mohamed Mahmoud Fouad

Lecturer of Neurology

Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

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Asmaa Mostafa Eissa

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List of Abbreviations

Abb.	Full term

ACTH..... Adrenocorticotropic hormones
ADL..... Activities of daily living
APCs ..... Antigen presenting cells
ApoE ..... Apolipoprotein E
BAEP ..... Brainstem auditory evoked potentials
BDNF..... Brain-Derived Neurotrophic Factor
CAMs ..... Cell Adhesion Molecules
CBC..... Complete blood count
CCL2 .....Chemokine ligand 2
CDMS ..... Clinically Definite MS
CIS..... Clinically Isolated Syndrome
CNPase……Cyclic nucleotide 3 phosphodiesterase
CNS……..Central nervous system
CRP……..…C-Reactive Protein
CSF……..Cerebrospinal Fluid
DTI……..Diffusion Tensor Imaging
EAE…….Experimental Autoimmune Encephalomyelitis
EBV…….Epstein - Barr virus
EDSS……..Expanded Disability Status Scale
EMA……European medicines agency
EPs……..Evoked Potentials
FA……..Fractional anisotropy
GFAP……Glial fibrillary acidic protein
GM-CSF……..Granulocyte Macrophage Colony-Stimulating Factor
HHV-4……...Herpes virus 4
HLA-DRB1…..Histocompatibility leucocytic antigen-DRB1
IFN- γ……Interferon gamma
IFN-β……Interferon beta

List of Abbreviations cont…

Abb.	Full term

IgG……..*Immunoglobulin G*
KFLC ..... *Kappa Free*
LFLC..... *Lambda Free Light Chains*
MBP..... *Myelin Basic Protein*
MD ..... *Mean diffusivity*
MHC ..... *Major histocompatibility complex*
MMPs..... *Matrix Metalloproteinase Proteins*
MOG……..*Myelin oligodendrocyte protein*
MRI..... *Magnetic Resonance Imaging*
MRS..... *Magnetic Resonance Spectroscopy*
MS..... *Multiple sclerosis*
MSIF..... *Multiple sclerosis international federation*
NAA ..... *N-acetyl-aspartate*
NABs..... *Neutralizing antibodies*
NAGM..... *Normally appearing grey matter*
NAWM..... *Normal appearing white matter*
N-CAM..... *Neuronal Cell Adhesion Molecule*
NETs..... *Neutrophil extracellular traps*
NFs ..... *Neurofilaments*
NLR ..... *Neutrophil/Lymphocyte ratio*
NMO ..... *Neuromyelitis optica*
NO..... *Nitric Oxide*
Nrf2..... *Nuclear factor (erythroid-derived 2)-like 2*
OCBs..... *Oligoclonal bands*
OCT..... *Optical Coherence Tomography*
ONDs……*Other neurological disorders*
PML ..... *Progressive multifocal leukoencephalopathy*
PPMS..... *Progressive MS*
RIS..... *Radiologically isolated syndrome*
RNFL..... *Retinal nerve fiber layer*

List of Abbreviations cont…

Abb.	Full term

ROS..... *Reactive oxygen species*
RRMS ..... *Relapsing remitting MS*
S1PR..... *Sphingosine 1-phosphate receptor*
SPMS..... *Secondary progressive MS*
SSEP..... *Somatosensory evoked potentials*
SWI ..... *Susceptibility-weighted Images*
TNF-α……*Tumour Necrosis Factor alpha*
TRECs..... *T-Cell Receptor Excision Circles*
VDRE..... *Vitamin D response element*
VEGF-A ..... *Vascular Endothelial Growth Factor-A*
WMLs……*White Matter Lesions*

Role of Neutrophil/Lymphocyte Ratio as an Indicator of Relapse in Multiple Sclerosis

Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the brain and spinal cord that is a common cause of serious physical disability in young adults. MS patients have various clinical presentations depending on the involved area of the central nervous system (CNS). The definite etiology of MS is still not known but most probably it is multifactorial. There is a debatae whether inflammation initiates neurodegeneration or neurodegeneration occurs independently of inflammation. The pathological findings in MS include inflammation, demyelination (degeneration), remyelination, axonal loss and glial scar formation (failure of repair). The main character of the inflammatory phase is associated with the destruction of the blood-brain barrier and local expression of pro-inflammatory cytokines and chemokines. It is believed that Neutrophil/Lymphocyte ratio (NLR) could be used as a simple, non-invasive, and low-cost marker in demonstrating acute inflammation. During the acute stage of MS, neutrophils are more active in the disease pathogenesis during relapse. This study aims to assess the NLR among a sample of RRMS patients during relapse (active stage) and remission (non-active stage) in order to investigate a potential role of NLR as a cost-effective simple predictor of MS activity in RRMS. Also, to assess the relation between NLR and the clinical features of the relapse. This study included 40 patients diagnosed with RRMS, 31 females and 9 males, age from 18-45 years with no other associated co-morbidities or other immunological disorders. Patients were recruited from neurology department of Nasser Institute Hospital with inclusion and exclusion criteria aiming to eliminate factors other than MS activity, which can alter the average values of NLR. Complete demographic and clinical data were gathered from the patients. NLR was calculated during the time of the relapse and after the remission. By comparison, NLR at the time of the relapse was significantly increased than NLR of remission of same patient (P-value <0.001).

Keywords: Multiple sclerosis (MS), central nervous system (CNS), Neutrophil/Lymphocyte ratio (NLR).

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the brain and spinal cord that is a common cause of serious physical disability in young adults ***(Dendrou et al., 2015).*** MS patients have various clinical presentations depending on the involved area of the central nervous system (CNS). The definite etiology of MS is still not known but most probably it is multifactorial ***(Guzel et al., 2015).*** There is a debatae whether inflammation initiates neurodegeneration or neurodegeneration occurs independently of inflammation ***(Losy, 2013).***

The pathological findings in MS include inflammation, demyelination (degeneration), remyelination, axonal loss and glial scar formation (failure of repair) ***(Bruck, 2005)***.The main character of the inflammatory phase is associated with the destruction of the blood-brain barrier and local expression of pro-inflammatory cytokines and chemokines ***(Gumus et al., 2015).***

MS disease activity is determined by clinical relapses and/or MRI activity and evidence of disease activity impacts prognosis and therapeutic options. Hence, it is important to discriminate between relapses and pseudorelapses. As relapses are clinically determined by worsening of already present symptoms or appearance of new symptoms, but pseudorelapses are temporary worsening of symptoms that are triggered by external factors such as physiologic or metabolic. Also some

chronic symptoms of MS as depression or fatigue may transiently worsen and are misinterpreted as a relapse ***(Lublin et al., 2014).***

Recent studies show significance of neutrophils infiltrating CNS prior to a relapse and their predominance in the blood at the formation of a new lesion. Hence, there is an increase in neutrophils activity and their related markers compared to healthy controls in MS patients during relapses ***(Pierson et al., 2016).***

It is believed that Neutrophil/Lymphocyte ratio (NLR) could be used as a simple, non-invasive, and low-cost marker in demonstrating acute inflammation. During the acute stage of MS, neutrophils are more active in the disease pathogenesis during relapse ***(Gumus et al., 2015; Pierson et al., 2016; Demirci et al., 2016).***

Aim of the Work

This study aims to assess the NLR among a sample of RRMS patients during relapse (active stage) and remission (non-active stage) in order to investigate a potential role of NLR as a cost-effective simple predictor of MS activity in RRMS. Also, to assess the relation between NLR and the clinical features of the relapse.

Chapter 1

OVERVIEW ON MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a chronic neurological disorder affecting CNS. It is classified as the most common neurological cause of disability in young adults. However the aetiology is not well understood, but most propably multifactorial involvement is the most convenient theory till now ***(Mckay et al., 2016)***. It is characterized by inflammation, demyelinaion, axonal loss and degeneration. There is a debatae about neurodegenerative character of the disease, whether inflammation initiates neurodegeneration or neurodegeneration occurs independent of inflammation ***(Losy, 2013).***

Various clinical presentations have been reported depending on the involved area of the CNS including physical, cognitive, and emotional disorders with different types of disease courses ***(Lublin, 2014)***. MS commonly affects young adults between the ages of 20 and 40 years, with a peak incidence at the age of 30 ***(Pena, 2013).*** Female to male ratio is 4:1 at adolescence, 2.5:1 in adulthood until age 45 to 49, and then 1:1.5 after the age of 50. This is indicative of a hormonal influence on MS risk or a gender defined genetic influence on immunologic activity ***(Cossburn et al., 2012)***.

A global survey in 2013 by multiple sclerosis international federation **(MSIF)** found that the estimated