Asymptomatic Cerebrovascular, Cognitive Dysfunctions and Mood Changes in Systemic Lupus Patients

Thesis

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الإعتلالات الدماغية و الإدراكية الغير ظاهرية والتغيرات المزاجية في مرضي الذئبة الحمراء

رسالة

توطئة للحصول على درجة الماجستير

فى الأ مراض الباطـــنة العامـــة

مقدمة من

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٢٠١٥


قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
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6-MP	6-mercaptopurine
Ab	Antibody
ACL	Aspartate aminotransferase
aCL	Anticardiolipin
ACR	The American College of Rheumatology
ACS	Acute confusional state
AED	Anti-Epileptic Drug
ALT	Alanine aminotransferase
ANA	Anti-Neclear Antibody
anti-Rib-P	Anti-ribosomal P
APL	Antiphospholipid antibodies
APS	Antiphospholipid Syndrome
AST	Aspartate aminotransferase
BDI	Beck Depression Inventory
BILAG	British Isles Lupus Assessment Group index
BLys	B lymphocyte stimulator
C3d	Complement component 3 d
CD	Cluster of Differentiation
CNS	Central Nervous System
CES-D	Center for Epidemiologic Studies Depression Scale
CBC	Complete blood count
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
CVD	Cerebrovascular disease
CXR	Chest X Ray
CYC	Cyclophosphamide
DNA	Deoxyribonucleic acid
dsDNA	Anti-double stranded deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual Criteria for Major depression
DTI	Diffusion Tensor Imaging
DWI	Diffusion-weighted imaging
EEG	Electro Encephalo Gram
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
Fc	Fragment crystallizable region

List of Abbreviations (Cont..)

FDA	Food and Drug Administration
GD S	Geriatric Depression Scale
GM	Grey matter
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
Hb	Hemoglobin
HDRS	Hamilton Depression Rating Scale
hep2	Human epidermoid carcinoma cell line 2
HLA	Human Leucocyte Antigen
IBM	The International Business Machines Corporation
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin G
IL	Interlukin
INR	International Normalized Ratio
IVIG	Intravenous immunoglobulin
JCV	John Cunningham virus
LAC	Lupus anticoagulant antibodies
LN	Lupus Nephritis
MCP-1	Monocyte chemoattractant protein-1
MDI	Major Depression Inventory
MMF	Mycophenolate mofetil
MMSE	Mini mental state examination
MPA	Mycophenolic acid
MR	Magnetic resonance
MRA	Magnetic resonance Angiograph
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Multiple Sclerosis
MTI	Magnetic Transfer imaging
NCS	Nerve conduction studies
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NP	Neuropsychiatric
NPSLE	Neuropsychiatric Systemic lupus erythematosus
NR2	N-methyl-D-aspartate Receptor 2

List of Abbreviations (Cont..)

NSAIDs	Nonsteroidal anti-inflammatory drugs
P value	Probability value
P/C	Protien /creatinine ratio
PCR	Polymerase Chain Reaction
PET	Positron emission tomography
PGA	Patient Global Assessment
PHQ	Patient Health Questionnaire
PLT	Platelets
PT	Prothrombin time
PTT	Partial thromboplastine time
QQ	Quantile-Quantile
RNA	Ribonucleic acid
S.cr	Serum creatinine
SD	Standard Deviation
SDS	Self-Rating Depression Scale
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosis Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SMMSE	Standardized Mini-Mental State Examination
SPECT	Single-photon emission computed tomography
SPSS	Statistical Package for the Social Sciences
STAT4	Signal Transducer and Activator of Transcription protein 4
TCD	Transcranial duplex
TIA	Transient Ischemic Attack
TNF	Tumor necrosis factor
TPI	Triosaphosphate isomeraze
TREX1	Three prime repair exonuclease 1
U/S	Ultrasound
Vs	Versus
WBC	White blood cell
WM	White matter

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototype of the systemic autoimmune connective tissue diseases. It affects 1 out of 2000 individuals worldwide of whom ≈ 90% are women. SLE is characterized by a storm of auto-antibodies and the release of inflammatory cytokines to most body tissue organs ***(Berthier and Kretzler, 2012)*.**

Although the specific cause of SLE is unknown, the development of the disease is the net result of the interplay of multiple factors including: genetic, ethnic, immuno-regulatory, hormonal and environmental factors ***(Rahman and Isenberg, 2008).***

Recently, several studies have indicated that the leading cause of morbidity and mortality in SLE patients is due to wide spread accelerated atherosclerosis and cerebrovascular diseases which are the pathological background of the neuropsychiatric (NP) SLE syndrome ***(Colombo and Cacciapaglia, 2009).***

A combination of chronic inflammatory and immune mediated mechanisms resulting in altered lipoprotein metabolism and the formation of proinflammatory and pro-oxidative lipids ***(Jara and Medina,2006).***

Contributory factors to accelerated atherosclerosis in SLE patients include increased levels of oxidized lipids, upregulation of adhesion molecules, and cytokines such as monocyte chemoattractant protein-1(MCP-1), tumor necrosis

factor (TNF), interferon-γ (IFN-γ), interleukin-1 (IL-1), and IL-12. Auto-antibodies are formed against the oxidized lipids and immune complexes in SLE patients, these antibodies play a role in the development of atherosclerosis in these patients ***(McMahon and Hahn, 2007).***

The overall survival of SLE patients has significantly improved over the last 50 years, from 74.8 to 94.8% and from 63.2 to 91.4%; 5-year and 10-year survival, respectively ***(Mak and Cheung, 2012).***

Neuropsychiatric (NP) disease occurs in as many as 30 – 56 % of all SLE patients. However, the diagnosis of neuropsychiatric SLE (NPSLE) remains difficult ***(Unterman and Nolte, 2011).***

NP lupus is associated with significantly increased morbidity and mortality in SLE patients. In 1999, the American College of Rheumathology (ACR) defined 19 distinct neuropsychiatric syndromes in SLE, including psychosis and depression ***(Ainiala and Hietaharju 2001).***

NP lupus is usually overlooked by the other more symptomatic disease manifestations, especially lupus nephritis (LN) which usually consumes the great clinical and laboratory concern. Subclinical NP lupus may be present early in the disease, however lack of the disease clinical signs and patients' unawareness delay the diagnosis "by the time we are argued regarding which immunosuppression should we use for LN remission induction, one should start cyclophosphamide for subclinical NP SLE ***(Petri and Orbai, 2012).***

Recent data has suggested that both renal and neuropsychiatric lupus disease negatively affect the overall 5-year survival rate, whereas the neuropsychiatric involvement did not change the 10-year survival rate***(Mak and Cheung, 2012).***

In studies where patients were screened with formal neuropsychiatric and sensitive psychiatric testing, the prevalence of mood disorder and cognitive impairment was high. Mild cognitive impairment was the most frequent abnormality among these patients, with only 3–5 % exhibiting severe cognitive impairment ***(Bertsias et al., 2010).***