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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
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Oligoclonal Band versus Chitinase 3 Like 1 Protein in CSF of Newly Diagnosed Relapsing Remitting Multiple Sclerosis

Thesis

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List of Contents

Title	Page No.
List of Tables	i
List of Figures	iii
List of Abbreviations	iv
Introduction	1
Aim of the Work	4
Review of Literature	
Multiple Sclerosis	5
Chitianse 3 Like 1 Protein	32
Subjects and Methods	47
Results	55
Discussion	67
Summary	74
Conclusion	76
Recommendations	77
References	78
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table I:	Mechanisms of Multiple Sclerosis	7
Table II:	Revised 2017 McDonald criteria for MS diagnosis:	26
Table III:	Summary of diseases associated with increased CHI3L1 levels.	35
Table IV:	Summary of the relationship between CHI3L1 and neurodegenerative diseases.	40
Table 5:	EDSS score for the study group.	55
Table 6:	Number of attacks for the study group.	55
Table 7:	Affected brain areas for the study group.	56
Table 8:	CSF oligoclonal bands for the study group.	56
Table 9:	Chitinase 3 like 1 protein in CSF for the study group.	57
Table 10:	Association between presence of CSF oligoclonal bands and sociodemographic parameters.	58
Table 11:	Association between CSF CHI3L1 and sociodemographic parameters.	59
Table 12:	Association between CHI3L1 and EDSS score in the studied patients.	60
Table 13:	Association between OCB and EDSS score in the studied patients.	60
Table 14:	Association between OCB and number of attacks in the studied patients.	61
Table 15:	Association between CHI3L1 and number of attacks in the studied patients.	62

List of Tables cont...

Table No.	Title	Page No.
Table 16:	Association between OCB and number of affected areas in the studied patients.	63
Table 17:	Association between CHI3L1 and number of affected areas in the studied patients.	64
Table 18:	Association between OCB and CHI3L1 in the CSF of studied patients.	65
Table 19:	The diagnostic characteristics of CHI3L1 in the studied patients.	66

List of Figures

Fig. No.	Title	Page No.
Figure I:	Effector T Cells in Multiple Sclerosis	14
Figure II:	The pathogenic role of B Cells in multiple sclerosis	19
Figure III:	Mechanisms in Progressive Multiple Sclerosis	20
Figure IV:	The Stages of Multiple Sclerosis	22
Figure V:	Oligoclonal band patterns using electrophoresis on polyacrylamide gels	29
Figure VI:	The roles of CLPs	34
Figure VII:	General regulatory pathways of CHI3L1 expression	39
Figure VIII:	The roles of CHI3L1 in the signaling pathways of neurodegenerative diseases	44
Figure 9:	Plate	52
Figure 10:	Chitinase 3 like 1 protein in CSF for the study group.	57
Figure 11:	Relation between Chitinase 3 like 1 protein in CSF and CSF oligoclonal bands.	65
Figure 12:	Roc curve of CHI3L1 in the studied patients.	66

List of Abbreviations

Abb.	Full term
AD	Alzheimer's disease
APCs	Antigen-presenting cells
AUC	Area under the curve
Aβ	Amyeloid beta
BBB	Blood-brain barrier
Breg	Regulatory B cells
CD	cluster of differentiation
CHI3L1	Chitinase 3 like protein 1
CHID1	Chitinase domain containing 1
CIMD	CNS immune-mediated disorders
CIS	Clinically isolated syndrome
CLPs	Chitinase like protein
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
CXCL	Chemokine (C-X-C motif) ligand
EBNA1	EBV nuclear antigen 1
EBV	Epstein- Barr virus
EDSS	Expanded Disability Status Scale
ELISA	Enzyme Linked Immunosorbent Assay
FLC	Free light chain
FoxP3	Forkhead box protein 3
GFAP	Glial fibrillary acidic protein
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GWASs	Genome-wide association studies
GzmA	Granzyme A
GzmB	Granzyme B
HLA	human leukocyte antigen

List of Abbreviations cont...

Abb.	Full term
IEF	Isoelectric Focusing
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IL2RA	Interleukin-2 receptor alpha gene
IL7RA	Interleukin-7 receptor alpha gene
IMSGC	International MS Genetics Consortium
iNOS	Inducible nitric oxide synthase.
IQR	Interquartile range
MAPK	Mitogen activated protein kinase
MBP	Myelin basic protein
MCP-1	Monocyte chemoattractant protein-1
MHC	Major histocompatibility complex
miRNA	MicroRNA
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
mtDNA	Mitochondrial DNA
MZ	Monozygotic
NASH	Non-alcoholic Steatohepatitis
NEDA	No Evidence of disease activity
Nf-L	Neurofilament light chain
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer
NMOSD	Neuromyelitis optica spectrum disorder
NS	Non significant
OCB	Oligoclonal bands
OD	Optical density
OVGP1	Oviductal glycoprotein 1

List of Abbreviations cont...

Abb.	Full term
PD	Parkinson's disease
PD-L1	Programmed death-ligand 1
PMS	Progressive MS
PPMS	Primary progressive MS
P-tau	Phosphorylated tau
RAGE	Receptor for Advanced Glycation End
RIS	Radiologically isolated syndrome
RNS	Reactive nitrogen species
ROC	Receiver Operating Characteristic
ROS	Reactive oxygen species
RRMS	Relapsing remitting MS
S	Significant
SCs	Symptomatic controls
SD	Standard deviation
SLE	Systemic Lupus Erythematous
Spearman's rho	Spearman's rank correlation coefficient
SPMS	Secondary progressive MS
SPSS	Statistical package for Social Science
STAT3	signal transducer and activator of transcription 3
Teffs	Effector T cells
TGF-β	Transforming growth factor β
Th	T helper
Th1	T-helper 1
Th17	T-helper 17
TNFα	Tumor Necrosis Factor alpha
Treg	Regulatory T Cell
UV	Ultraviolet

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune-mediated demyelinating disease of the central nervous system (CNS) that is usually associated with varying degrees of progressive disability. In most patients the early stages of disease, known as relapsing remitting MS (RRMS) are characterized by clinical exacerbations, or relapses, caused by autoreactive immune cells that traffic into the CNS, resulting in focal inflammation and demyelination often visible as gadolinium-enhancing lesions on magnetic resonance imaging (MRI). Relapses are followed by periods of clinical remission as inflammation resolves and remyelination occurs ***(Harris et al., 2017).***

Investigation of cerebrospinal fluid (CSF) in the diagnostic work-up in suspected MS patients has regained attention in the latest version of the diagnostic criteria due to its good diagnostic accuracy and increasing issues with misdiagnosis of MS based on over interpretation of neuroimaging results. The hallmark of MS-specific changes in CSF is the detection of oligoclonal bands (OCB) which occur in the vast majority of MS patients.

The current laboratory methods for detection of CNS immunoglobulin synthesis are immunoglobulin G (IgG)-index and gel isoelectric focusing with visual detection of oligoclonal bands (OCB), of which OCB is considered the gold standard

(Link and Huang, 2006). OCB positivity requires a minimum of two unique IgG bands in CSF, which are not present in serum. Both methods, however, have weaknesses. The relevance of IgG index in MS diagnostics has previously been questioned due to low sensitivity, OCB have been reported in other primary and secondary CNS immune-mediated disorders (CIMD) that may clinically mimic MS such as CNS lupus, various forms of CNS vasculitis, neurosarcoidosis, antiphospholipid syndrome, CNS infections, CNS lymphoma and neuromyelitis optica spectrum disorder (NMOSD). In addition, OCB is time consuming, expensive, merely qualitative and due to its visual interpretation, it is prone to inconsistent results ***(Franciotta and Lolli, 2007).***

Therefore, the further search for other biomarkers which are less complicated and less subjective to detect is of great importance in order to improve the diagnosis and therapy of MS ***(Deisenhammer et al., 2019).***

Chitinase 3–like protein 1(CHI3L1), has attracted growing attention as a marker of ongoing inflammation and oncogenic transformation. This secreted glycoprotein, belongs to the 18-glycosyl-hydrolase family of proteins but lacks glycolytic activity. Although its biological functions are not fully understood, it is expressed by many cell types, including macrophages, neutrophils, chondrocytes, endothelial cells, microglia, and astrocytes ***(Bhardwaj et al., 2015).***

In MS brain tissue, CHI3L1 is expressed in astrocytes in white matter plaques and in normal appearing white matter, and it is also expressed in microglia in MS lesions ***(Hinsinger et al., 2015).*** In addition, CHI3L1 mediate increased immune cell trafficking across the blood brain barrier. CHI3L1 is hypothesized to play a role in chronic inflammation and tissue remodeling ***(Correale et al., 2011).***

Aim of the Work

The aim of this work was to try to assess the diagnostic accuracy of CHI3L1 versus IgG oligoclonal bands (OCBs) in the CSF of newly diagnosed RRMS patients in an attempt to throw light on a new simpler non subjective potential diagnostic marker in MS.