



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



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شبكة المعلومات الجامعية التوثيق الإلكتروني والميكرو فيلم



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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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CXCL13 Level in Children with Acute and Relapsing Demyelinating Disorders of the Nervous system

Thesis

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in Pediatrics*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا نك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
ADEM	<i>Acute disseminated encephalomyelitis</i>
AE	<i>Autoimmune encephalitis</i>
ACD	<i>Albumin cytological dissociation</i>
ANEC	<i>Acute necrotizing encephalopathy of childhood</i>
AIDP	<i>Acute inflammatory demyelinating polyneuropathy</i>
AMAN	<i>Acute motor axonal neuropathy</i>
AMPA	<i>A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor</i>
AMSAN	<i>Acute sensorimotor axonal neuropathy</i>
APC	<i>Antigen presenting cells</i>
BBB	<i>Blood brain barrier</i>
BCA-1	<i>B cell-attracting chemokine 1</i>
BLR1	<i>Burkitt's lymphoma receptor 1</i>
CBC	<i>Complete blood count</i>
CIDP	<i>Chronic inflammatory demyelinating polyradiculoneuropathy</i>
CMV	<i>Cytomegalovirus</i>
CNS	<i>Central nervous system</i>
CSF	<i>Cerebrospinal fluid</i>
CT	<i>Computed tomography</i>
CXCL13	<i>C-X-C motif ligand 13</i>
DC	<i>Dendritic cells</i>
Diag	<i>Diagnosis</i>
DWI	<i>Diffusion-weighted imaging</i>
EAE	<i>Experimental autoimmune encephalomyelitis</i>
EEG	<i>Electroencephalography</i>
EMG	<i>Electromyography</i>
ERK	<i>Extracellular Signal-Regulated Kinase</i>
F	<i>Female</i>
FDC	<i>Follicular DC</i>
GABAB r	<i>Gamma-aminobutyric acid-B receptor</i>
GAD65	<i>Glutamic acid decarboxylase 65</i>
GBS	<i>Guillain-Barré syndrome</i>
GC	<i>Germinal centers</i>
GlyR	<i>Glycine receptor</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>GPCRs</i>	<i>G protein-coupled receptors</i>
<i>HIV</i>	<i>Human immunodeficiency virus</i>
<i>HS</i>	<i>Highly significant</i>
<i>IVIG</i>	<i>Intravenous immunoglobulin</i>
<i>IVPMP</i>	<i>Intravenous pulse methylprednisolone</i>
<i>LETM</i>	<i>Longitudinally extensive transverse myelitis</i>
<i>LP</i>	<i>Lumbar puncture</i>
<i>M</i>	<i>Male</i>
<i>MAPK</i>	<i>Mitogen-activated protein kinase</i>
<i>MFS</i>	<i>Miller fisher syndrome</i>
<i>MOG-Ab</i>	<i>Myelin oligodendrocyte glycoprotein antibody associated disease</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>MS</i>	<i>Multiple sclerosis</i>
<i>MV</i>	<i>Mechanical ventilation</i>
<i>N</i>	<i>Number</i>
<i>NB</i>	<i>Neuroborreliosis</i>
<i>NINDS</i>	<i>National institute of neurological disorders and stroke</i>
<i>NMDAR</i>	<i>N-methyle-D-aspartate receptor</i>
<i>NMOSD</i>	<i>Neuromyelitis optica spectrum disorders</i>
<i>NS</i>	<i>Non significant</i>
<i>NCV</i>	<i>Nerve conduction velocity</i>
<i>ON</i>	<i>Optic neuritis</i>
<i>PCNSL</i>	<i>Primary central nervous system lymphoma</i>
<i>PLEX</i>	<i>Plasma exchange</i>
<i>S</i>	<i>Significant</i>
<i>SD</i>	<i>Standard deviation</i>
<i>SIADH</i>	<i>Syndrome of inappropriate antidiuretic hormone secretion</i>
<i>TB</i>	<i>Tuberculosis</i>
<i>TBI</i>	<i>Traumatic brain injury</i>
<i>Ttt</i>	<i>Treatment</i>
<i>TM</i>	<i>Transverse myelitis</i>
<i>TNF</i>	<i>Tumor necrosis factor</i>
<i>VEP</i>	<i>Visual evoked potentia</i>
<i>WHO</i>	<i>World Health Organization</i>

INTRODUCTION

Acquired demyelinating disorders of central nervous system (CNS) are rare childhood disorders and cause significant physical and cognitive disabilities (*Absoud et al., 2011*). These disorders are caused by immune-mediated destruction of the white matter of brain, optic nerve, and spinal cord (*Gulati et al., 2015*). Multiple sclerosis (MS), optic neuritis (ON), transverse myelitis (TM), clinically isolated syndrome (CIS), Devic disease, and acute disseminated encephalomyelitis (ADEM) are collectively known as acquired demyelinating syndromes (*Longer-Gould et al., 2011*).

Guillain-Barre syndrome is an immune-mediated inflammatory demyelinating disease of the peripheral nervous system. It is the most common cause of acute paralytic neuropathy (*Esposito and Longo, 2017; Sejvar et al., 2011; Sladky, 2004 and Jones, 2000*).

CNS autoimmune encephalitis, characterized by the presence of antibodies binding to brain receptors, ion channels, and related proteins (*Vincent et al., 2011 and Leypoldt et al., 2015*) is now also increasingly recognized in children (*Armanque et al., 2012 and Wong-Kisiel et al., 2012*).

Many of these disorders manifest most commonly in childhood or adolescence, whereas others more typically occur in adults (*Waldman et al., 2014 and Graus et al., 2016*).

Chemokines are a family of small molecular weight proteins known for their ability to act as chemoattractants, thereby functioning to induce the migration of nearby responding cells. These secreted proteins, together with a host of other extracellular mediators, including growth factors and eicosanoids, are key modulators of inflammation by controlling complex interaction networks via autocrine and paracrine mechanisms. Multiple diseases have been associated with aberrant production of chemokines and cytokines, including infectious diseases, chronic inflammation, and autoimmune disorders (***von Hundelshausen et al., 2017 and Proost et al., 2017***).

They are also involved in the expression of adhesion molecules, cytokine secretion, phagocytosis, matrix metalloproteinases release, T-cell activation and differentiation, neuronal development, synaptic transmission, angiogenesis and apoptosis. In multiple sclerosis, chemokines together with adhesion molecules, may facilitate the passage of autoreactive T cells and macrophages through the blood-brain barrier, and mediate movement of inflammatory cells to lesion sites in the CNS (***Cheng and Chen, 2014***).

The C-X-C motif chemokine ligand 13 (CXCL13) is a chemokine produced by antigen-presenting cells such as follicular dendritic cells and macrophages. Via its receptor—CXCR5—it serves as a chemoattractant, homing B cells into secondary lymphoid organs (***Van Burgel et al., 2011 and Klimatcheva et al., 2015***).

CXCL13 has been shown as an essential chemokine in the recruitment of B cells into the CNS in various neuroinflammatory conditions such as MS and viral and bacterial infections, as well as in malignant, autoimmune, and chronic inflammatory diseases (*Fujimori et al., 2014; Schmidt et al., 2011 and Khadmi et al., 2011*).

Cerebrospinal fluid (CSF) CXCL13 was suggested to be a highly specific and sensitive diagnostic marker for neuroborreliosis (*Senel et al., 2010 and Schmidt et al., 2011*), but is also raised in other neuroinfectious and inflammatory disorders (*Kother et al., 2016 and Alvarez et al., 2013*). Recently, an increasing focus has been on CXCL13 as a potential therapeutic target in these diseases (*Huber and Irani, 2015*).

CXCL13 is found in human blood, plasma and serum and high CXCL13 levels have been associated with primary Sjögren's syndrome and systemic lupus erythematoses (*Fava et al., 2011; Nocturne et al., 2015 and Fang et al., 2017*).