New Updates in Pathogenesis, Diagnosis And Their Impact on Management In Multiple Sclerosis

Essay

Submitted for partial fulfillment of Master Degree in
Neuropsychiatry

By

Amira Abd El-Samea Basiouny
M.B.,B.Ch

Supervised by

Prof. Dr. Taha Kamel Alloush
Professor of Neuropsychiatry
Faculty of Medicine, Ain Shams University

Dr. Salma Hamed Khalil
Assistant Professor of Neuropsychiatry
Faculty of Medicine, Ain Shams University

Dr. Ahmed Ali Ibrahim El-Bassiouny
Lecturer of Neuropsychiatry
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2010

كليـة الطـب
جامعـة عيـن شمـس
2010

Acknowledgment

First and foremost I would like to thank "Allah" for every thing. This would not be achieved without the support of "Allah".

I would like to expess my deepest gratitude to **Prof. Dr. Taha Kamel Alloush,** Professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for his constant help, encouragement, meticulous constructive advice, keen supervision to me.

I am greatly honored to express my deep gratitude to **Dr. Salma Hamed Khalil,** Assistant Professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, she gave me much of her time, experience and endless support that can not be expressed in words.

I wish to express my great gratitude and ultimate thanks to **Dr. Ahmed Ali Ibrahim El-Bassiouni,** Lecturer of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for his

encouragement, help, without his help this work would never be completed.

Amira Abd El-Samea Basiouny

Contents

List Of Abbreviations

ADA	Adenosine Deaminase
ADEM	Acute Disseminated Encephalomyelitis
ADP	Adenosine Diphosphate
AMP	Adenosine Monophosphate
AHSCT	Autologous Haematopoietic Stem-Cell Transplantation
APC	Antigen Presenting Cells
ATG	Anti-Thymocyte Globulin
BBB	Blood-Brain Barrier
BEAM	Carmustine, Etoposide, Cytosine-Arabinoside, and Melphalan
BOLD	Blood Oxygenation-Level-Dependent
CBC	Complete Blood Count
CCSVI	Chronic Cerebrospinal Venous Insufficiency
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
DAB	Diaminobenzidine
DNA	Deoxyribonucleic Acid
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
EBV	Epstein-Barr Virus
FDA	Food and Drug Administration

FH2	Dihydrofolic acid
FH4	Folinic acid
FLAIR	Fluid-Attenuated Inversion Recovery
FMRI	Function Magnetic-Resonance
GA	Glatiramer Acetate
GABA	γ-amino Butric Acid
Gd	Gadolinum
GFAP	Glial Fibrillary Acid Protein
HHV-6	Human Hypervirus 6
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSC	Hematopoietic Stem Cells
ICAM	Intracellular Adhesion Molecule
IFN	Interferon
IG	Immunoglobulin
IL	Interleukin
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MAG	Myelin-Associated Glycoprotein
MBP	Myelin Basic Protein
MEP	Motor Evoked potiential
MHC	Major Histocompatibility
MIMS	Mitoxantrone In Multiple Sclerosis
MRI	Magnetic resonance imaging

MS	Multiple Sclerosis
MTR	Magnetization Transfer Ratio
NAbs	Neutralizing Antibodies
OCBs	Oligoclonal Bands
OMgp	Oligodendro cyte Myliniglycoprotein
PCR	Polymerase Chain Reaction
PG	Prostaglandins
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
RNA	Ribonucleic Acid
RRMS	Relapsing/Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
TBI	Total Body Irradiation
TGF	Transformer Growth Factor
TH	T Helper
TNF	Tumour Necrosis Factor
VEPs	Visual Evoked Potentials
VCAM	Vascular Cell Adhesion Molecule
VDR	Vitamin D Receptors
WM	White Matter

List of Tables

List of Figures

Figure No.	Title	Page No.

List of Figures *(Cont...)*

Figure No.	Title	Page No.

List of Figures *(Cont...)*

INTRODUCTION

Disease-modifying treatments of multiple sclerosis allow a reduction of diseases activity visible on magnetic resonance imaging (MRI), a reduced probability of relapse in the short term and potentially a reduced rate of accumulation of irreversible disability in the long-term. Several arguments support the idea that initiating treatment early should proved greater clinical benefit than when treatment is started later in the course of the disease ***(Tintoré et al, 2008)***.

An important goal of treatment is to prevent accumulation of irreversible neurological disability and in particular to prevent conversion to a secondary progressive course, initiating effective treatment early in the disease course in order to reduce relapse rate and the underlying inflammatory process may delay irreversible neurological damage and conversion to a secondary progressive course ***(Fisniku et al., 2008)***.

The current therapeutic paradigm in multiple sclerosis consists of starting with an immunomodulatory treatment, either an interferon-β or glatiramer acetate, and then advancing up a therapeutic pyramid in case of inadequate controlled. The successive steps of this pyramid might be firstly to switch between first-line therapies, and then to escalate to a more aggressive

therapy such as immuosuppression with mitoxantrone or alemtuzumab, or natalizumab. All these latter agents have been shown to reduce mean relapse rates by 60% or more ***(Anu et al., 2007)***.

Escalation therapy in multiple sclerosis recommended first-line therapy with an interferon-β or glatiramer acetate, followed by a switch to the other class of therapy in case of inadequate response and then escalating to mitoxantrone or natalizumab if the switch was not successful ***(MSTCG, 2008)***.

Induction therapy represents a more aggressive approach in which powerful immunosuppressant drugs are used right from the beginning to tackle the disease process hard and early ***(Jayne, 2008)***.

Recently, three additional studies compared the efficacy of glatiramer acetate with that of high-dose subcutaneous interferon-β found that the efficacy of glatiramer acetate is comparable to that of interferon-β 1b on a wide range of clinical and MRI outcome ***(Sorensen et al., 2008)***.

At recombinant interferon-β has been detected, the presence of neutralizing antibodies (NAbs) to varying degrees, in all clinical trials of these preparations in multiple sclerosis ***(Sørensen et al., 2005)***.

Promoting remyelination is an important goal in the treatment of multiple sclerosis for a number of reasons. From a structural point of view, remyelination restores the integrity of white matter tracts in the nervous system and functionally improves axonal conduction by restoring the normal salutatory mode of rapid conduction leading to recovery to normal neurological function. Importantly, remyelination re-establishes signaling between the axon and the myelin sheath. This is important, since trophic factors released from myelin are believed to play a key role in maintaining axonal survival ***(Kassmann and Nave, 2008)***.

Currently, at least four potential therapies to promote remyelination in multiple sclerosis are under investigation. These are cell transplantation, inhibition of the trophic factor LINGO-1, prolactin and glatiramer acetate ***(Chandran et al., 2008)***.

AIM OF THE WORK

Review the new data about pathogenesis and diagnosis and treatment of multiple sclerosis for proper management of similar cases.