Multiple sclerosis
Secondary prevention

Essay

Submitted for partial fulfillment of
M.Sc. Degree in Neuropsychiatry

Presented by

Salem Taha El Sayed

M.B., B.Ch.

Faculty of Medicine - Ain Shams University

Supervised by

Prof. Dr. Amira Ahmed Zaki Dwedar

Professor & Chairman of Neuropsychiatry department
Ain Shams University

Prof. Dr. Mahmoud Hemeda El Rakawy

Professor of Neuropsychiatry
Ain Shams University

Prof. Dr. Azza Abd El Naser Abd El Aziz

Professor of Neuropsychiatry
Ain Shams University

Ain Shams University
2009

CONTENTS

Acknowledgment

First of all, I would like to thank God, for allowing me to preform this work.

Special thanks and my profound appreciation to **Prof. Dr. Amira Ahmed Zaki Dwedar** , Professor and Chairman of Neuropsychiatry department, Faculty of medicine, Ain Shams University, for here endless patience and guidance. This work could not have reached its goal without her support. Starting from the main idea till reaching the final goal, she has stood as the motivating power of each aspect of this study.

I would like to express my gratefulness and sincere appreciation to **Prof. Dr. Mahmoud Hemeda El Rakawy,** Professor of Neuropsychiatry, Faculty of medicine, Ain Shams University, for his supervision, valuable remarks and suggestions that helped me in the final production of this work.

I wish also to express my thanks to **Prof. Dr. Aza Abd El Nasr Abd El Aziz** , Professor of Neuropsychiatry, Faculty of medicine, Ain Shams University, for here help and encouragement.

Finally, I would like to express my deepest thanks and gratitude to all my professors, colleagues in Neuropsychiatry department, Faculty of medicine and family members specially my mother, brother and my wife who stood beside me throughout this work giving me their support, sympathy and guidance.

List Of Abbreviations

ACTH	Adrenocorticotrophic Hormone
AHSCT	Autologous Haematopoietic Stem-Cell Transplantation
APC	Antigen Presenting Cells
ATG	Anti-Thymocyte Globulin
AUC	Area Under Curve
BBB	Blood-Brain Barrier
BEAM	Carmustine, Etoposide, Cytosine-Arabinoside, and Melphalan
CBC	Complete Blood Count
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
DMT	Disease Modifying Therapy
DNA	Deoxyribonucleic Acid
DPK	Diphosphate Kinase
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
FAE	Fumaric-Acid Ester
FDA	Food and Drug Administration
FH2	Dihydrofolic acid
FH4	Folinic acid
FLAIR	Fluid-Attenuated Inversion Recovery

FSH	Follicle-Stimulating Hormone
GA	Glatiramer Acetate
Gd	Gadolinum
GnRH-a	Gonadotropin-Releasing Hormone agonist
GMPS	Guanosine Monophosphate Synthetase
HIV	Human Immunodeficiency Virus
HPRT	Hypoxanthine Phosphoribosyltransferase
HSC	Hematopoietic Stem Cells
ICAM	Intracellular Adhesion Molecule
IFN	Interferon
IG	Immunoglobulin
IMPDH	Inosine Monophosphate Mehydrogenase
LFT	Liver function test
LH	Luteinizing Hormone
LVEF	Left Ventricular Ejection Fraction
MAG	Myelin-Associated Glycoprotein
MBP	Myelin Basic Protein
MEP	Motor Evoked potiential
MESNA	Mercaptoethane Sulfonate
MHC	Major Histocompatibility
MIMS	Mitoxantrone In Multiple Sclerosis
MOG	Myelin Oligodendrocyte Glycoprotein
MPK	Monophosphate Kinase
MRI	Magnetic resonance imaging

MP	Mercaptopurine
MS	Multiple Sclerosis
NIH	National Institutes of Health
PCR	Polymerase Chain Reaction
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive-Relapsing Multiple Sclerosis
RNA	Ribonucleic Acid
RRMS	Relapsing/Remitting Multiple Sclerosis
SNRS	Scripps Neurologic Rating Scale
SPMS	Secondary Progressive Multiple Sclerosis
SSEP	Somato-Sensory Evoked Potential
TBI	Total Body Irradiation
TFT	Thyroid function test
TGF	Transformer Growth Factor
TH	T Helper
TNF	Tumour Necrosis Factor
TPMT	Thiopurine-S-Methyltransferase
TRAIL	Tumor necrosis factor-Related Apoptosis Inducing Ligand
VCAM	Vascular Cell Adhesion Molecule
VDR	Vitamin D Receptors
XO	Xanthine Oxidase

Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system (CNS) and the most common disabling neurological disease of young adults with a lifetime risk of 1 in 400.

Multiple sclerosis affects nearly 300,000 people in the United States. Although people of all ages and ethnicities can have multiple sclerosis, it is more common in women than in men, and in whites than in blacks or Asians. More than 2.5 million people worldwide are estimated to be affected by multiple sclerosis with approximately 25,000 people are newly diagnosed with this disease every year.

Despite intensive efforts in finding the source of the disease, no etiologic agent for MS has been identified. The disease presumably can be exacerbated by hormonal changes during the postpartum period. Some argue that MS could be a heterogeneous disorder triggered by several different environmental agents. In fact, only 1 of every 4 MS attacks is associated with an intercurrent infection.

The ultimate goal of treatment of multiple sclerosis should be to cure the disease however MS is a dynamic disease, with almost constant lesion formation and a progressive clinical course leading to physical disability.

So, in order to avoid the disability that accumulates with every relapse, treatment should start as early as possible within the first 2 weeks of the onset of the relapse.

And since a major part of the pathogenesis of the disease has been ascribed to a deviation of the immune system Thus, apart from glucocorticosteroids, immunosuppressive and immunomodulating agents were among the very first drugs available against MS.

Immunomodulating agents used for disease modification including Interferon beta, Glatiramer acetate and Humanized monoclonal antibodies (Natalizumab, Alemtuzumab, Rituximab and Daclizumab) that are newly promising therapies.

Immunosuppressive agents are inhibitors of crucial components of the immune system causing generalized immune dysfunction, they are among the very first drugs available against MS and were used off-label, but at least, in part, they were used successfully.

Among the immunosupressive agents used in treatment of MS are Cyclophosphamide, Azathioprine, Mitoxantrone, Methotrexate, Mycophenolate mofetil, Cladribine, Sirolimus/Temsirolimus and others.

Other agent shows some benefiet in treatment of MS as Statins, vitamin D and a newly promising procedure of stem cell transplantation.

Aim of the work

To highlight various models of disease modifying therapy used in secondary prevention of different courses of MS.

Courses and Pathogenesis of MS

Multiple Sclerosis was first described by ***Charcot and Vulpian in 1866*** . MS is an inflammatory disease of the Central Nervous System. The inflammation causes patches of damage called plaques or lesions that are predominantly located in the white matter of the CNS. At the site of an inflammatory lesion the myelin sheath gets lost in a process called demyelination. When the myelin is lost, the transmission of nerve impulses is slowed or even stopped. To some extent, the myelin sheath around the axons can be repaired after the inflammation has resolved. This process is called remyelination and is triggered by oligodendrocytes.

If there are not enough oligodendrocytes present at the site of the lesion, remyelination may not take place or only happen partially. In this case, the nerve will continue to function in an abnormal way, but the axon might remain undamaged for a long time. The lost myelin can also be replaced with scar tissue, which gave MS its name: ‘‘multiple’’ many and ‘‘sclerosis’’ scar forming. Once axons have become scarified they do not fully regain their former function ***(Hemmer et al., 2002)***.

As the disease progresses, oligodendrocytes and, ultimately, the axons themselves are destroyed, which leads to a worsening of disease symptoms. There is overwhelming evidence that the destruction is caused by the body’s own immune system indicating that MS is an autoimmune disease ***(Voskuhl, 2002).*** However recent

evidence suggests that axonal loss responsible for irreversible disability occurs already early in the disease course ***(Hemmer et al., 2002).***

MS affects probably more than 1 million people around the world—including twice as many women as men ***(Voskuhl, 2002).***

Most people experience their first signs or symptoms between ages 20 and 40. A significantly higher incidence of the disease is found in the northernmost latitudes of the northern and the southern hemispheres compared to southernmost latitudes ***(Hogancamp et al., 1997).***

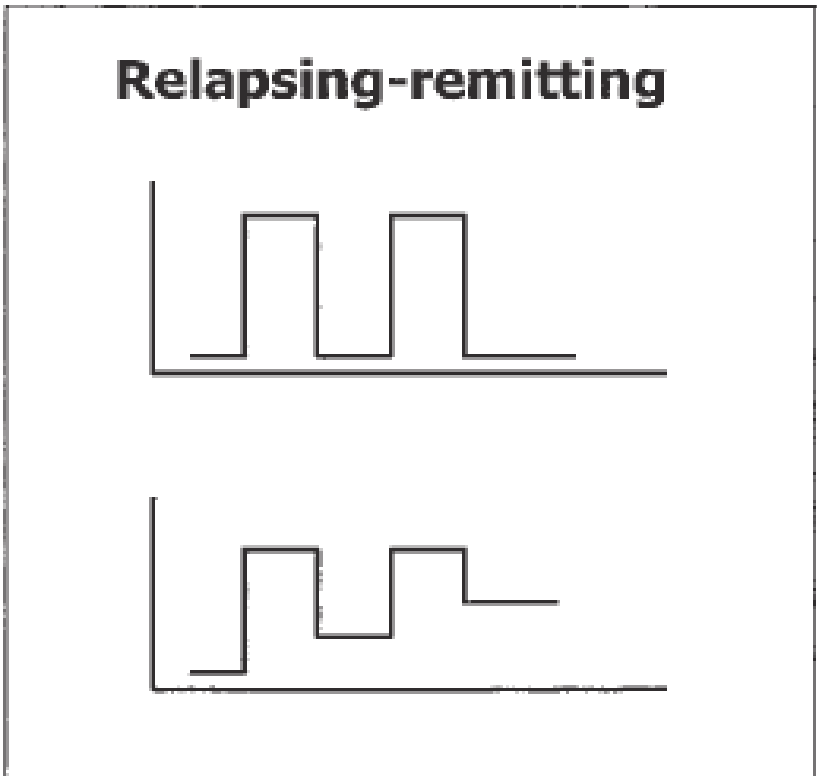
Kieseier and Hartung (2003) discussed four different courses of the disease variable from one patient to another, the disease may be:

A. Relapsing/Remitting Multiple Sclerosis (RRMS):

Most people presenting with MS (about 80%) are first diagnosed with Relapsing/Remitting Multiple Sclerosis. In this form, patients experience a series of relapses (also known as exacerbations) followed by complete or partial disappearance of the symptoms (remissions) until another relapse occurs. There can be weeks to decades between relapses. Relapses can last for days, weeks or months and recovery can be slow and gradual or almost instantaneous. During remission the patient fully or partially recovers from the deficits acquired during the relapse.

The following graph demonstrates two typical courses of RRMS.

Fig. 1: ***Course of RRMS***



(Reipert, 2004).

B. Primary Progressive Multiple Sclerosis (PPMS):

About 10–20% of people presenting with MS suffer from Primary Progressive MS. This form is characterized by a gradual progression of the disease involving a decline in the patient's physical abilities with only short periods where the decline seems to stop with some minor relief.