Clinical, Neuro-Immunological, Neurophysiological, Neuro-Radiological Studies in Multiple Sclerosis

Thesis
Submitted in partial fulfillment
For M.D. Degree in Neurology

Alaa Eldin Mahmoud M.B., B.Ch

M.Sc. Neurology & Psychological Medicine

Supervised By

Prof. Dr. Mervat Moustafa

Professor of Neurology Cairo University

Prof. Dr. Malaka Fouad

Professor of Clinical Pathology Cairo University

Prof. Dr. Tarek Tawfiek

Professor of Neurology Cairo University

Prof. Dr. Helmy Abdulhamid

Professor of Radiology Cairo University

Faculty of Medicine Cairo University 2008

Acknowledgement

First, and foremost, all thanks to **GOD**, most gracious and most merciful.

I am extremely grateful to **Prof. Dr. Mervat Moustafa**, Professor and head of the department of Neurology, Faculty of Medicine Cairo University, for her continuous guidance, meticulous supervision and valuable suggestions, saving no effort or time to read every ward in this work.

I would like to express my deepest gratitude and sincere thanks to **Prof. Dr. Tarek Tawfiek**, Professor of Neurology, Faculty of Medicine Cairo

University for his continuous guidance and valuable advice for enriching this work. I appreciate his hard support to me, which has given a powerful push helping this research to come to reality

I wish to express my sincere thanks to **Prof. Dr. Malaka Found**, Professor of clinical Pathology. Faculty of Medicine, Cairo University for her enthusiastic cooperation, assistance, and efforts during this work giving me the help and encouragement throughout the work.

Much thanks to **Prof. Dr. Helmy Abdulhamed**, Professor of Radiology, Faculty of medicine Cairo University for his help, guidance assistance and faithful supervision during this work.

I am very appreciative to **Prof. Dr. Farouk Koura**, Professor of Neurology, Faculty of Medicine Cairo University for giving me the help and encouragement throughout the work.

I would like also to declare my thanks to **Prof. Dr Obsis Madkour**, **Prof. Dr. Mohammed Mountaser**, **Prof. Dr. Mahmoud Alam**, **Prof. Dr. Saher Hashiem**, **Prof. Dr. Hassan Elwan**, **Prof. Dr Mohamed El-Tawdi** and **Prof. Dr. Ahmed Talat** Heads of the Neurology department, Faculty of Medicine Cairo University, for their assistance, guidance, and help throughout the work.

Much thanks to **Prof. Dr. Ann Abdelkader**, professor of Neurophysiology, Faculty of Medicine, Cairo University for her help and cooperation.

Finally I wish to extend my deepest appreciation to all my colleagues in Neurology Department and Neurophysiology Unit Faculty of Medicine, Cairo University who helped me a lot in making this work possible.

Alaa Eldin M.
2008

Contents

Introduction

```
Review of literature 10
Epidemiology and Etiology 11
     Pathophysiology <u>23</u>
        Pathology 29
       Pathogenesis 33
   The immune system <u>51</u>
     Clinical picture 71
        Diagnosis 81
  Course and prognosis 89
      Investigations 95
  Subjects and Methods 118
         Results 137
       Discussion 219
Summary and Conclusion 239
       References 247
       Appendices 277
    Arabic Summary 294
```

List of Tables

- Table (1) Age distribution among patients of the present study. 138
- Table (2) Age distribution among patients of both sexes in the present study. 138
- Table (3) Shows correlation between current age, age of onset and number of relapses. 139
- Table (4) Sex distribution among patients of the present study. 141
- Table (5)Shows correlation between sex and age of onset of multiple sclerosis attacks among patients of the present study. 141
- Table (6) Duration of illness among patients of the present study. 143
- Table (7)Distribution of the duration of illness among patients of the present study. 143
- Table (8) Shows the frequency of positive parental consanguinity in our patients. 145
- Table (9) Shows correlation between consanguinity against current age, age of onset and sex. 145
- Table (10) Shows the positivity of family history among our patients. <u>146</u>
- Table (11) Shows the geographic distribution among patients within this study. 146
- Table (I2) Shows the distribution of precipitating factors in the first relapse among our patients. 147
- Table (13) Shows correlation between precipitating factors against current age and age of onset among our patients. 148
- Table (14) Shows correlation between precipitating factors against sex. 148
- Table (15) Shows number of patients with mono and poly-symptomatic presentation at the onset of the disease 149
- Table (16) Shows the distribution of symptomatic presentation among our patients. <u>150</u>
- Table (17) Sites of affection in-patients is, this study. 153
- Table (18) Shows correlation between current age and age of onset and number of symptoms at presentation. 155
- Table (19) Shows correlation between sex & consanguinity against mono and poly- symptomatic presentation among our patients. 155
- Table (20) Mean and Std. Deviation of EDSS scores among patients. 156
- Table (21) EDSS scores among patients in the present study. 157
- Table (19) Shows correlation between EDSS scores and clinical parameters. 159

- Table (23) Shows correlation between EDSS scores and the duration of illness among patients in the present study. 160
- Table (24) Distribution of MRI lesions in-patients of this study. 162
- Table (25) Shows mean and standard deviation of results of p100 latency. 164
- Table (26) Shows the results of VEP in the study. 164
- Table (27) Shows mean and standard deviation of results of BAEP. 166
- Table (28) Shows the results of BAEP in this study. 166
- Table (29) Shows mean and standard deviation of results of SSEP. 167
- Table (30) Shows mean and standard deviation of total proteins, albumin and albumin quotient of patients in the present study. 169
- Table (31) Shows mean and standard deviation of C_3 , C_4 and ATT in serum of patients of the present study. 170
- Table (32) Shows mean and standard deviation of lgG, 1gM, IgA, lgG index as well as IgM index in-patients of the present study. 172
- Table (33) Shows mean and standard deviation of TNF and IL1 in both serum and CSF of patients in the present study. 174
- Table (34) Shows correlation study between age of patients and serum albumin, total proteins, as well as albumin quotient 175
- Table (35) Shows correlation study between the duration of illness against serum albumin and proteins, as well as albumin quotient among patients in the present study. 176
- Table (36) Shows results of a comparative study between serum albumin and proteins, as well as albumin quotient against sex, consanguinity and Precipitating factors. 177
- Table (37) Shows correlation studies between EDSS scores against Serum albumin and total proteins, as well as albumin quotient. 178
- Table (38) Shows correlation study between age of patients and C3, C4 and ATT results. 179
- Table (39) Shows correlation study between the duration of illness and serum complement (C3, C4) as well as ATT. 180
- Table (40) Shows correlation study between clinical results and serum complement (C3, C4) as well as ATT. 181
- Table (41) Shows correlation studies between EDSS scores against Serum albumin and total proteins, as well as albumin quotient. 182
- Table (42) Shows correlation studies between Age of Patients against serum immunoglobulins, IgG index and 1gM index. 183

- Table (43) Shows correlation study between the duration of illness and serum immunoglobulins (IgG, IgA and 1gM), IgG index and 1gM index among patients in the present study. 184
- Table (44),(45) and (46) Shows correlation study between sex, consanguinity and precipitating factors againest serum immunoglobulins (IgG, IgA and 1gM), IgG index and 1gM index among patients in the present study. 185,186
- Table (47) Shows correlative study between EDSS scores and means of IgG, IgM, IgG index and 1gM index. 187
- Table (48) Shows correlation study between age of patients against TNF $\alpha 1$ and ILl in CSF and serum. . 188
- Table (49) Shows correlation study between the duration of illness againest Serum and CSF TNFα1 and IL1. 189
- Table (50) &(51) Shows correlation study between sex, consanguinity and precipitating factors againest Serum and CSF TNFα1 and IL1.191,190
- Table (52) Shows correlation between EDSS scores against TNFα1 and ILl in CSF and serum. 192
- Table (53) Shows results of correlation study between P100 Latency versus age, duration of illness and EDSS scores. 193
- Table (54) Shows results of correlation study between P100 Latency versus sex, consanguinity and precipitating factors among patients in the present study. 194
- Table (55) Shows correlation between SSEP and Age of patients. 195
- Table (56) Shows correlation between SSEP & EDSS. 196
- Table (57) Shows correlation between SSEP and duration of illness. 196
- Table (58) Shows correlation between SSEP scores versus sex, consanguinity and precipitating factors among patients in the present study. 197
- Table (59) Shows correlative study between BAEP and age of patients. 198
- Table (60) Shows comparison between BAEP and duration of illness. 199
- Table (61) Shows correlation between BAEP and EDSS scores. 200
- Table (62) and (63) Shows correlative study between BAEP versus sex, consanguinity and precipitating factors among patients in the present study. 201,202

- Table (64) Shows correlative study between P_{100} latency against IgG, IgM, IgA, IgG index, 1gM index, C3, C_4 and ATT. 203
- Table (65) Shows comparison between means of TNFα1 both in serum and CSF and BAEP studies. 204
- Table (66) Shows Correlative studies comparing TNFα1 levels and means of VEP and SSEP studies. 205
- Table (67) Shows correlation between results of VEP versus BAEP and SSEP (latency). 206
- Table (68) Comparative study between results of SSEP and EAEP. 207
- Table (69) Shows levels of TNFα1 and ILl in controls and patients. 208

Abbreviations

MS ---- Multiple Sclerosis.

CSF — Cerebrospinal fluid.

Gd-DTPA —-Gadolinium-diamine-triamnic- penta acetic acid.

PVP — Perventricular plaques.

VEP — Visual evoked potential.

BAEP — Brainstem & auditory evoked potential.

SEP — Somatosensory evoked potential.

BBB — Blood Brain Barrier.

MRI — Magnetic Resonance Imaging.

SPECT — Single Photon Emission Computed Tomography.

CT — Computed Tomography.

FS — Functional Systems.

EDSS — Expanded Disability Status Scale.

NPN — Negative-Positive- Negative (Waves of VEP).

TNF — Tumor necrosis Factor.

IL1 — Interleukin 1.

C3 — Complement 3.

C4 — Complement 4.

ATT — Alpha 1 antitrypsin.

IgA — Immunoglobulin A.

IgM — Immunoglobulin M.

IgG — Immunoglobulin G.

IgD — Immunoglobulin D.

IgE — Immunoglobulin E.

HLA — Human leucocytic antigen.

MRS — Magnetic Resonance Spectroscopy.

MHC — Major Histocompatibility complex.

CD — Cell of differentiation.

T4+ — T helper, inducer lymphocytes.

T8+ — T-suppressor, cytotoxic lymphocytes.

TGF — Tumor growth factor.

LN — Lymph node.

MALT — Mucosa associated lymphoid tissue.

NK — Natural killer cells.

TCR — T- cell receptor.

IFN — Interferon.

APCS — Antigen presenting cells.

SD — Standard deviation.

Da — Dalton.

MBP — Myelin basic protein.

RT — Repetition time.

TE — Echo time.

RR — Remitting-Relapsing.

Q — Albumin quotient.

PD — Proton Density (of MRI).

T1 wt. Image — Tl Relaxation time weighted image (of MRI).

T2 wt. Image — T2 Relaxation time weighted image (of MR1).

REVIEW OF LITERATURE

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology and Etiology

- Multiple sclerosis is the most common untreatable neurological disease that causes disability among young adults. It is defined as an inflammatory demyelinating disease, which affects different parts of the central nervous system through the destruction of myelin sheath (which is a fatty material that insulate nerves and allowing the nerve to transmit its impulses rapidly). Resulting in an inflammatory response that produces any number of symptoms including: blurred vision, staggering gait, numbness, dizziness, tremors, slurred speech, bowel and bladder problems, sexual impotence in men and paralysis, (O'Connor P. et al 1994).
- Multiple sclerosis has a very specific geographic distribution around the world. As a significantly higher incidence of the disease is observed in the northern latitudes of the Northern Hemisphere as compared to the southern latitudes. While in the Southern Hemisphere this gradient is reversed, (meaning that there is an increased rate of multiple sclerosis as we get away from the equator). However, there are a few notable exceptions to this previous general pattern of distribution. Found in Japan where surveys have shown multiple sclerosis uncommon and in Israel where it is found common, regardless to the location of both countries from the equator. (Kurtzke J.F. 1995)
- Therefore, the world is divided into three large clusters:
 - Low incidence areas: including Arabia, Tropical countries and Asia.

- Medium incidence areas: including southern regions of the U.S.A.
- High incidence areas: including northern U.S.A, northern European countries and Australia.

(Adams R.D. et al 1997).



Fig. (1) Geographic distribution of multiple sclerosis worldwide Coated from (Fox C.M.Adams R.D. et al 2004).

Prevalence and Incidence:

- Compston D.A. et al (1993) calculated the prevalence of multiple sclerosis worldwide to be from 10 to 200 cases per 100,000 Populations. They assured that multiple sclerosis had a prevalence of less than 1 per 100.000 in equatorial Africa, from 6 to 20 per 100.000 in the southern United States and southern Europe and from 30 to 150 in Canada and northern U.S.A.
- Lauer K. et al (1994) estimated the prevalence of multiple sclerosis in the United Kingdom to be from 90 to 150 per 100.000 populations, compared to that of Finland, which reached up to 200 per 100.000 populations.