

# TRACE ELEMENTS IN CONVULSIVE DISORDERS

## THESIS

Submitted for Partial Fulfillment of

M.D. Degree in Pediatrics

BY

Nahla Moustafa Adly Ahmed Heshmat

M.B. B.Ch., M.S.

618-92845

NP.M

SUPERVISORS

Prof. Dr. Rabah Mohamed Shawky

Professor of Pediatrics

Ain Shams University

Prof. Dr. Farida Ahmed Farid

Professor of Pediatrics

Ain Shams University

Ass. Prof. Dr. Abd El-Aziz Mohamed Kamal

Assistant Professor of Occupational Medicine

Ain Shams University

Faculty of Medicine

Ain Shams University

1991



46289



**Dedication...**

*To the soul of my great teacher*

***Professor Dr. Mahmoud Essawy***

*whom I'll always remember.*



## ACKNOWLEDGEMENTS

*I wish to express my gratitude to **Prof. Dr. Rabah Mohamed Shawky**, Professor of Pediatrics, Ain Shams University, for giving me the privilege of working under her supervision and for her faithful encouragement and guidance.*

*I feel deeply indebted to **Prof. Dr. Farida Ahmed Farid**, Professor of Pediatrics, Ain Shams University, for her considerable help, assistance and valuable remarks throughout this work.*

*I sincerely acknowledge the help and kindness of **Ass. Prof. Dr. Abd El-Aziz Mohamed Kamal**, Assistant Professor of Occupational Medicine, Ain Shams University; **Prof. Jean Marie Haguenoer**, Director of Laboratoire De Toxicologie Professionnelle - Institut Du Medecine, Du Travail, Du Nord De La France - Lille, and **Dr. Assem Badawy**, Lecturer of Toxicology, Ain Shams University, for their cooperation in the laboratory part of the work.*

*I greatly appreciate the help of **Dr. Moustafa El Houssinie Moustafa**, Lecturer of Community and Environmental*

*Ain Shams University, for preparing the statistical analysis of this work.*

*I heartily thank my professors, my colleagues and all the members of my family for their understanding and support throughout this whole work and always.*

*Last, but by no means least, I thank the patients and their parents for their cooperation and patience and serving as subjects for this study.*

**Nahla Moustafa Heshmat**

## CONTENTS

|  | Page |
|--|------|
| List of Abbreviations                                    | i    |
| List of Tables   | ii   |
| List of Figures  | iv   |
| 1. Introduction and Aim of Work                          | 1    |
| 2. Review of Literature                                  | 3    |
| Trace Elements   | 3    |
| Zinc   | 3    |
| Copper   | 12   |
| Magnesium  | 18   |
| Manganese  | 23   |
| Convulsive Disorders                                     | 26   |
| Terminology  | 26   |
| Classification of seizures                               | 27   |
| Classification of epilepsies and epileptic syndromes     | 36   |
| Conditions in which recurrent convulsions occur commonly | 43   |
| Therapy with anticonvulsant drugs                        | 44   |
| Febrile convulsions                                      | 52   |
| Trace Elements in Convulsive Disorders                   | 56   |
| Zinc in convulsive disorders                             | 56   |
| Copper in convulsive disorders                           | 67   |
| Magnesium in convulsive disorders                        | 69   |
| Manganese in convulsive disorders                        | 73   |

|                                  | Page |
|----------------------------------|------|
| Cobalt in convulsive disorders   | 75   |
| Iron in convulsive disorders     | 77   |
| Selenium in convulsive disorders | 80   |
| 3. Subjects and Methods          | 82   |
| 4. Results                       | 93   |
| 5. Discussion                    | 142  |
| 6. Summary and Conclusion        | 171  |
| 7. Recommendations               | 175  |
| 8. References                    | 177  |
| 9. Arabic Summary                |      |

## LIST OF ABBREVIATIONS

|                          |   |
|--------------------------|---|
| ANOVA                    | Analysis of variance                      |
| Ca                       | Calcium                                   |
| CaBP                     | Calcium binding protein                   |
| CNS                      | Central nervous system                    |
| CSF                      | Cerebrospinal fluid                       |
| Cu                       | Copper                                    |
| 25 (OH) D                | 25 hydroxy cholecalciferol                |
| 1,25 (OH) <sub>2</sub> D | 1,25 dihydroxy cholecalciferol            |
| EAAs                     | Excitatory amino acids                    |
| EEG                      | Electroencephalogram                      |
| EIA                      | Enzyme immunoassay                        |
| GABA                     | Gamma-aminobutyric acid                   |
| GAD                      | Glutamic acid decarboxylase               |
| K                        | Potassium                                 |
| LEM                      | Leucocyte endogenous mediator             |
| LMNL                     | Lower motor neuron lesion                 |
| Mg                       | Magnesium                                 |
| Mn                       | Manganese                                 |
| n                        | Number of subjects                        |
| Na                       | Sodium                                    |
| Na-K-ATPase              | Sodium-potassium-adenosine triphosphatase |
| PLP                      | Pyridoxal phosphate                       |
| S-Cu                     | Serum copper                              |
| SD                       | Standard deviation                        |
| S-Mg                     | Serum magnesium                           |
| S-Mn                     | Serum manganese                           |
| S-Zn                     | Serum zinc                                |
| UMNL                     | Upper motor neuron lesion                 |
| Zn                       | Zinc                                      |



## LIST OF TABLES

| No.                         | Title   | Reference                   | Page |
|-----------------------------|---|-----------------------------|------|
| <b>Review of Literature</b> |   |                             |      |
| 1.                          | The possible causes of zinc deficiency  | Standstead et al., 1976     | 9    |
| 2.                          | Causes of hypomagnesemia according to different age groups                                | Burman and McLaren, 1982    | 20   |
| 3.                          | Classification of seizures  | Dreifuss et al., 1981       | 27   |
| 4.                          | International classification of epilepsies and epileptic syndromes                        | Tharp, 1987; Dreifuss, 1989 | 37   |
| 5.                          | Conditions in which recurrent convulsions occur commonly                                  | Huttenlocher, 1987 b        | 43   |
| 6.                          | Drugs used in control of convulsive disorders   | Menkes, 1985                | 46   |
| 7.                          | Pharmacokinetics of major antiepileptic drugs   | Holmes, 1989                | 47   |
| <b>Results</b>              |   |                             |      |
| 1.                          | Clinical and laboratory data of epileptics  |                             | 115  |
| 2.                          | Clinical and laboratory data of the controls  |                             | 118  |
| 3.                          | Comparison between epileptics and controls as regards their serum level of trace elements |                             | 119  |
| 4.                          | Effect of age on serum level of trace elements in controls                                |                             | 120  |

| <b>No.</b> | <b>Title</b>   | <b>Page</b> |
|------------|--|-------------|
| 5.         | Effect of age on serum level of trace elements in epileptics   | 121         |
| 6.         | Comparison between serum level of trace elements of epileptics and that of age and sex matched controls  | 122         |
| 7.         | Comparison between treated and untreated epileptics and controls as regards their serum level of trace elements  | 123         |
| 8.         | Comparison between epileptics treated with different antiepileptic drugs, untreated epileptics and controls as regards their serum level of trace elements | 124         |
| 9.         | Effect of the type of seizure on serum level of trace elements   | 125         |
| 10.        | Effect of the etiology of seizures on serum level of trace elements  | 126         |
| 11.        | Relation between severity of epilepsy and serum level of trace elements  | 127         |
| 12.        | Relation between the time interval from last seizure to sampling, and serum level of trace elements  | 128         |
| 13.        | Relation between presence of mental retardation in epileptics and serum level of trace elements  | 129         |
| 14.        | Correlation between serum Zn, Cu, Mg and Mn  | 130         |

## LIST OF FIGURES

| No.                         | Title  | Page |
|-----------------------------|--|------|
| <b>Subjects and Methods</b> |  |      |
| 1.                          | Method of additions  | 88   |
| <b>Results</b>              |  |      |
| 1.                          | Comparison between serum Cu of epileptics and controls   | 137  |
| 2.                          | Effect of age on serum Cu of controls  | 138  |
| 3.                          | Effect of age on serum Cu of epileptics  | 139  |
| 4.                          | Comparison between serum Zn of treated epileptics, untreated epileptics and controls; and comparison between serum Cu of treated epileptics, untreated epileptics and controls | 140  |
| 5.                          | The effect of time interval between last seizure and sampling on serum Mn.   | 141  |

# *Introduction and Aim of the Work*

## INTRODUCTION AND AIM OF THE WORK

### Introduction

The minerals required for physiologic functions may be divided into 2 groups:

- Macrominerals which are required in amounts greater than 100 mg/day. They are calcium, chloride, magnesium, phosphorus, potassium and sodium.
- Microminerals (trace elements) which are required in amounts less than 100 mg/day. They are chromium, copper, iodine, iron, manganese, molybdenum, selenium, zinc, cobalt. Silicon, vanadium, nickel, arsenic, fluoride, and tin have been shown to be essential in various species and may be required in humans (*Mayes, 1988*).

The possible involvement of trace elements in convulsive disorders has been given more attention in recent years (*Pei and Koyama, 1986*). Trace elements which have been involved in convulsive disorders are: Zinc, copper (*Taylor and Ghose, 1986*), manganese (*Carl et al., 1986*), selenium (*Wark et al., 1984*) and cobalt (*Craig and Colasanti, 1986*) and magnesium (*Tolde et al., 1987*).

### **Aim of the Work**

Our aim is to evaluate the state of zinc, copper, magnesium and manganese in different convulsive disorders affecting children, and to evaluate the effect of anticonvulsant therapy on these elements.

# *Review of Literature*