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بالرسالة صفحات لم ترد بالاصل

Study of some Immuno-Genetic Markers for Insulin Dependent Diabetes Mellitus Among Siblings of Insulin Dependent Diabetes Mellitus Patients in Alexandria

Thesis

submitted to The Faculty of Medicine,
University of Alexandria
In partial Fulfilment of the Requirements
of the degree of

DOCTOR
In
INTERNAL MEDICINE

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ACKNOWLEDGEMENT

I'd like to express my deep gratitude for all those who shared either practically or morally in the achievement of this thesis.

My efforts would not have succeeded without the guidance understanding and fatherly encouragement of Prof. Dr. Fahmy Amara, Professor of Internal Medicine, and Head of Diabetes and Metabolism Unit, Faculty of Medicine, Alexandria University.

I am deeply indebted to Prof. Dr. Samir Helmy Assaad-Khalil, Professor of Internal Medicine, Unit of Diabetes & Metabolism Alexandria University, who spent a lot of his effort and time generously in a kind supervision and meticulous assistance arousing in me a sparkling interest in the subject of this study. He initiated the idea & plan of this research and supervised and implemented all steps and details related to the patients, their families, the sera and international cooperation. I will remain always grateful.

I whish to express my deep feeling and appreciation to Prof. Dr. Omar El-Farouk Elazzouni, Professor of pediatrics, Faculty of Medicine, Alexandria University, for his support and assistance.

I do sincerely express may gratitude to Prof. Dr. Thomas Dyrberg, Hagedron Research Institute, Denmark, for his practical contribution and for the great effort he has exerted to accomplish this work. My deep gratitude is also extended to Dr. Birigitte Koch Michelsen, Hagedorm Research Institute, Denmark for her indispensable contribution in this work.

It is a great honour to express my deepest gratitude, my sincerest feelings and my cordial appreciation to Ass. Prof. Dr. Myriam Abou-Seif Helmy, Ass. Prof. Of Clinical Pathology, for suggesting and planning the immunological study and her special practical contribution, to her I am especially indebted.

Also, I'd like to acknowledge the great effort of Ass. Prof. Dr. Faten Anis Kamel, And Ass. Prof. Dr. Kamal Fouad, Ass. Professors of Community Health for their contribution in the epidemiologic and statistical analysis of the study.

I am also grateful to Dr. Hassan Andel Fattah Director of Egypt Health Insurance Authority and to Dr. Said Abdel Ghany Director of sporting Student Hospital for allowing me to include the children with diabetes & their families in the study. Also I owe to Dr. Omima El Menawy for her help in this concern.

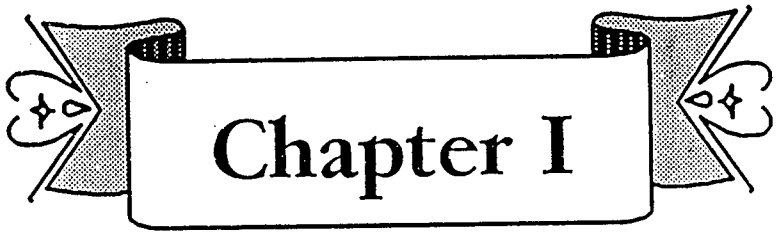
I owe to the assistance offered by the department in Internal Medicine, Unit of Diabetes & Metabolism namely, Prof. Dr. Mabaheg Souka, Professor of Internal Medicine, Prof. Dr. Mohamed El-Bahrawy Professor of Internal Medicine, and Assist Prof. Dr. Talaat Abdel Aty, to them I am especially indebted.

Lastly, and not least, I would like to express my deepest thanks to my wife for her sacrifices, help and encouragement.

CONTENTS

LIST OF ABBREVIATIONS

IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NDDG	National Diabetes Data Group
WHO	World Health Organization
FPG	Fasting Plasma Glucose
FBS	Fasting Blood Sugar
PPBS	Post-Prandial Blood Sugar
GADA	Glutamic Acid Decarboxylase Autoantibodies
ICA	Islet-Cells Antibodies
IAA	Insulin Autoantibodies
ICA_{512}	Islet-Cell $Antigen_{512}$
MHC	Major Histocompatibility Compex
(NOD) Mice	Non Obese Diabetic Mice
BB Rats	Bio Breading Rats
HLA	Human Leucocytic Antigens
EMC	Encephalomyocarditis
I-A	Region associated antigen
JDF Units	Juvenile Diabetes Foundation units



INTRODUCTION

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TYPE 1 DIABETES MELLITUS (IDDM)

Type 1 diabetes mellitus is defined by the presence of classical symptoms of diabetes such as thirst, polyuria, wasting, and/or ketoacidosis and the necessity for insulin treatment not only to control the hyperglycemia and symptoms but to prevent the spontaneous occurrence of ketoacidosis.[1]

Usually the fasting blood or plasma glucose concentration is unequivocally elevated (> 140 mg/dl or > 7.8 mmol) and glucose and ketones are present in the urine. Glucose tolerance testing is rarely necessary to make a diagnosis. The diagnosis of type 1 diabetes mellitus usually is made on the basis of symptoms and these biochemical parameters alone.[1] However, the new diagnostic criteria for diabetes mellitus have been modified from those previously recommended by the NDDG or WHO, and for epidemiological studies, estimates of diabetes prevalence and incidence should be based on a FPG $\geq$ 126 mg/dl.[2]

Type 1 diabetes mellitus is the most common form of diabetes in children and young adults, particularly those of northern European origin. The disease has a much lower incidence among persons of

Oriental or Native American heritage. Although the incidence increases with age until adolescence and then declines, the disease can have its onset at any age.[1]

Some patients especially those with diabetes onset before they are 30 years old, receive insulin treatment on the basis of elevated blood glucose levels without their proneness to development of ketosis having ever been documented. Unless these patients subsequently develop ketosis or have insulin treatment withdrawn, it may be difficult to determine retrospectively whether they are indeed insulin-dependent and, therefore, whether they do have type 1 (insulin-dependent) diabetes mellitus. Since Type 2 diabetes does occur in children and young adults as well as in older persons, at the time of diagnosis, attempts should be made to determine and document proneness to ketosis. Without such documentation, a definitive diagnosis of type 1 diabetes mellitus may be problematic.[3]

In such patients, an indication of the extent of the insulin deficiency may be obtained by determining the fasting serum concentration of C-peptide. A provocative test with measurement of serum C-peptide after intravenous administration of glucagon probably provides the most sensitive means of determining whether the insulin deficiency in such patients is of the severity characteristic of type 1 diabetes mellitus. Patients who require insulin treatment for the control of hyperglycaemia but not for the prevention of ketosis should not be classified as having type 1 diabetes mellitus.[3]

Autoimmune destruction of pancreatic β-cells is the most common cause of type 1 diabetes mellitus. Evidence of this autoimmune process includes the presence of islet cell antibodies, insulin autoantibodies, and antibodies to glutamic acid decarboxylase (GAD) or 64-kilodalton protein. Abnormal titres of these antibodies may predate the onset of type 1 diabetes mellitus, but after onset the titres tend to fall, although less for GAD than for ICA or IAA. Thus, verification of the autoimmune nature of the disease by searching for these antibodies in patients who have had type 1 diabetes mellitus for some time may not be possible.[4-6]

Autoimmune β-cell destruction is more frequent in patients with certain HLA types, but the particular types associated with the disease vary by racial and ethnic group.[7] Type 1 diabetes mellitus rarely develops in subjects with aspartic acid at the 57 position of the HLA-DQB1 allele. Although this and other HLA relations represent risk factors, their sensitivity and specificity for diagnosis are low and therefore not clinically useful.[8]

The factors that initiate autoimmune pancreatic β-cell destruction are unknown. While viruses and chemical toxins have been suggested as initiating agents, specific agents have only rarely been identified as causes of type 1 diabetes mellitus.[9]