Cognitive and Academic abilities in Children and Adolescents with Type 1 Diabetes Mellitus

Thesis

Submitted for the Partial Fulfillment of Master Degree in Pediatrics

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2018

Who used to encourage me

to go for every success

especially this one

Proud of You always

&

Blessed by having You

a Martyr in Heaven now

Your memory will be eternal..

Dedicated with love to say:

" Thank You "

First and foremost, I feel always indebted to ALLAH, the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to *Professor Dr. / Mona Salem,* Professor of Pediatrics - Faculty of Medicine- Ain Shams University for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.

I am delighted to express my deepest gratitude and thanks to *Professor Dr. / Nancy Samir Elbarbary,* Professor of Pediatrics, Faculty of Medicine, Ain Shams University**,** for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.

I am deeply thankful to *Professor Dr. / Soheir Helmy ElGhonemy,* Professor of Psychiatry, Faculty of Medicine, Ain Shams University**,** for her great help, active participation in the practical part and kind guidance.

I would like to express my hearty thanks to **my lovely *Family*** and **my colleague *Ereny El Kess*** for their great support till this work was completed.

Last but not least my sincere thanks and appreciation to **all patients** participated in this study.

Christine Adel Salama Mikhail.

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Abbreviations

Abb.	Full term
AAIDD	*American Association of Intellectual and Developmental Disabilities*
ACEi	*ACE inhibitors*
ACR	*Albumin-creatinine ratio*
ADA	*American Diabetes Association*
ADC	*Apparent diffusion coefficient*
AER	*Albumin Excretion Rate*
AGEs	*Advanced glycation end products*
ARB	*Angiotensin-receptor blockers*
APA	*American Psychological Association*
BG	*Blood glucose*
BMI	*Body mass index*
CDC	*Conventional dendritic cells*
CKD	*Chronic kidney disease*
CKD-EPI	*Chronic Kidney Disease Epidemiology Collaboration*
CMS	*Children's Memory Scale*
CSII	*Continuous subcutaneous insulin infusion*
CT	*Computed tomography*
CVD	*Cardiovascular disease*
DAG	*Diacylglycerol*
DCCT	*Diabetes Control and Complications Trial*
DHC	*Diabetes healthcare*
DKA	*Diabetic ketoacidosis*
DM	*Diabetes mellitus*
DN	*Nephropathy*
DPP-4	*Dipeptidyl peptidase 4*
DR	*Retinopathy*
DSM	*Diagnostic and Statistical Manual of Mental Disorder*

List of Abbreviations (Cont...)

Abb.	Full term
ESRD	*End stage renal disease*
FDA	*Food and Drug Administration*
GAD	*Glutamic acid decarboxylase*
GAD65	*Glutamic acid decarboxylase*
GFR	*Glomerular filtration rate*
GLP-1	*Glucagon-like peptide-1*
HHS	*Hyperosmolar hyperglycemic state*
HLA	*Human Leukocyte Antigen*
HNF-4α	*Hepatocyte Nuclear Factor*
ID	*Intellectual disability*
IMT	*Intima-Media thickness*
ISPAD	*International Society for Pediatric and Adolescent Diabetes*
LDL	*Low-density lipoprotein*
LDs	*Learning disabilities*
MODY	*Maturity-onset diabetes of the young*
MRI	*Magnetic resonance imaging*
NeuroD1	*Neurogenic differentiation*
OGTT	*Oral glucose tolerance test*
PAK	*Pancreas-after-kidney*
pdx1	*Pancreatic and duodenal homeobox 1*
PID	*Proportional-integral-derivative control*
SPK	*Simultaneous pancreas-kidney*
T1DM	*Type 1 diabetes mellitus*
Th1	*Helper cell*
UAER	*Urinary albumin excretion rate*
WHO	*World Health Organization*
WISC	*Wechsler Intelligence Scale for Children*

Abstract

Objective: To assess the cognitive functions and academic performance in children and adolescents with type 1 diabetes mellitus (T1DM) and identify the most possible risk factors affecting them.

Methods: This is a cross sectional study of 90 children and adolescents with T1DM attending Pediatric Diabetes Clinic, Children's Hospital, Ain Shams University were classified into 3 matched groups as follows: newly diagnosed, controlled and uncontrolled T1DM. All the included patients were subjected to detailed medical history with especial emphasis on the most possible risk factors affecting brain functions. An IQ test using Wechsler intelligence scale for children (WISC) was performed for all the 3 groups and overall academic grades were recorded, based on the scores obtained in the main subjects (Arabic, English and Mathematics).

Results: Total number of all patients (n=90); 30 in each group, their mean age was 11.42 ± 3.50 years old with mean age at diagnosis was 7.57 ± 3.42 years old and median duration of T1DM was 4 years with 10% of the patients were admitted to the hospital by DKA. Comparison between the 3 groups of type 1 diabetic patients according to diabetes-related variables revealed that, patients with controlled T1DM were found to be significantly the lowest HA1c level (mean 7.84 ± 1.5) (P-value = 0.000) and the earliest age of diagnosis (mean 5.7 ± 2.95) (P-value = 0.000) with the longest duration of T1DM (median 5.5 years) (P-value = 0.000), they got the best IQ test grades (P-value = 0.017) and academic grades (P-value = 0.000) in all subjects compared with other groups of uncontrolled and newly diagnosed type 1 diabetic patients. Analysis of the IQ and academic grades in relation to the studied parameters revealed that; high levels of HA1c are associated with cognitive and academic affection rather than the age at diagnosis, duration of the disease and frequency of hypoglycemia in children and adolescents with T1DM.

Conclusion: Metabolic derangements associated with T1DM affect brain integrity in children and adolescents which in turn affect their cognitive and academic functions. The most important risk factors are late diagnosis, chronic hyperglycaemia and DKA occurrence.

Keywords: T1DM; Cognitive and Academic abilities.

INTRODUCTION

A constant supply of glucose to the brain is critical for normal cerebral metabolism Thus; it is not surprising that developing brains in early childhood are more susceptible to metabolic insult, particularly those resulting from perturbations in blood glucose levels. Type 1 diabetes mellitus (T1DM) is among the most common chronic diseases of childhood and the condition most likely to cause the greatest swings in amplitude in blood glucose on an hour-to hour basis ***(Fergus, 2015).***

Children with T1DM perform less well in a range of cognitive domains compared with control groups, which some studies have linked to their history of glycemic control ***(Lin et al., 2010)***. However, the impact that these cognitive differences have on academic achievement is unclear. Even though some studies have found no difference in academic abilities between children with T1DM and control subjects, others have reported lower academic performance in children with T1DM ***(Wodrich et al., 2011).***

The clinical factors inherent in T1DM responsible for these conflicting results remain unclear. There is limited information on the relationship between degree of glycemic exposure and academic abilities in children and young people with T1DM ***(Hannonen et al., 2012).***

Results from both longitudinal and cross-sectional studies show that T1DM is associated with mild-to-modest decrements in cognitive function. Domains of psychomotor speed, mental flexibility, attention, and general intelligence are most commonly affected. Data from prospective studies suggest that hypoglycemia is not a risk factor for cognitive decline; however, this may not be true for children with young age at the onset of diabetes ***(Moheet et al., 2015).***

Acknowledgment of diabetes-associated cognitive decrements can help to improve understanding of patients' symptoms and guide management. Future challenges are to establish the importance of screening for cognitive impairment in people with diabetes, to identify those at increased risk of accelerated cognitive decline at an early stage, and to develop effective treatment ***(Koekkoek et al., 2015).***

Achieving tighter glycemic control early in childhood may be important for minimizing risk for suboptimum cognitive and academic development ***(Semenkovich et al., 2015).***

AIM OF THE WORK

The aim of this work is to:

Assess ***Cognitive functions*** and ***Academic performance*** in children and adolescents with T1DM and their relation to the diabetes-related variables (age at diagnosis, duration of the disease, HA1c level, frequency of hypoglycaemia and DKA occurrence).

Chapter 1

TYPE 1 DIABETES MELLITUS

Definition and Description

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both ***(International Society of Pediatric and Adolescent Diabetes; ISPAD, 2014).***

The chronic hyperglycemia of diabetes is associated with relatively specific long term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD) ***(American Diabetes Association; ADA, 2012).***

Classification; (Table 1)

The ADA classification of DM encompasses 4 groups:

I. Type 1 DM
II. Type 2 DM
III. Other specific types of diabetes
IV. Gestational diabetes

Table (1): Classification of diabetes mellitus

I. Type I-DM: (B-cell destruction, usually leading to absolute insulin deficiency) A. Immune mediated. B. Idiopathic.	**II. Type II-DM:** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance).
III. other specific types	
A. Genetic defects of β-cell function: 1. MODY3 (Chromosome 12, HNF1α) 2. MODY1 (Chromosome 20 HNF4α) 3. MODY2 (Chromosome7glucokinase) 4. Other very rare forms of MODY (e.g. MODY4: Chromosome 13, insulin Promoter factor-1, MODY6: Chromosome9, carboxyl ester lipase) 5. Transient neonatal diabetes 6. Permanent neonatal diabetes 7. Mitochondrial DNA 8. Others	**B. Genetic defect in insulin action** 1.Type A insulin resistance 2.Leprechaunism 3.Rabson-Mendenhall syndrome 4.Others
C. Diseases of exocrine pancreas 1.Pancreatitis 2.Truama/ pancreatectomy 3.Neoplasia 4.Cystic fibrosis 5.Haemochromatosis 6.Fibrocalculous pancreatopathy 7.Others	**D. Endocrinopathies** 1.Acromegaly 2.Cushing's syndrome 3.Glucagonoma 4.Pheochromocytoma 5.Hyperthyroidism 6.Somatostatinoma 7.Aldosteronoma 8.Others
E. Drugs or chemical- induced 1.Vacor 2.Pentamidine 3.Nictotinic acid 4.Glucocorticoids 5.Thyroid hormone 6.Diazoxide 7.B-adrenegic agonist 8.Thiazides 9.Dilantin 10.γ-interferon 11.Others	**F. Infections** 1.Congenital rubella 2.cytomegalo virus 3.Others
G. Uncommon forms of immune-mediated Diabetes 1."Stiff-man" syndrome 2.Anti-insulin receptor antibodies 4.Others	**H. Other genetic syndromes sometimes Associated with diabetes** 1.Down syndrome 2.Klinfelter syndrome 3.Turner syndrome 4.Wolfram syndrome 5.Friedreich's ataxia 6.Huntington's chorea 7.Laurence-Moon-Biedle syndrome 8.Myotonic dystrophy 9.Porphyria 10.Prader-Willi syndrome 11.Others
IV. Gestational diabetes.	

MODY: Maturity onset diabetes of the young, **HNF-4α:** Hepatocyte Nuclear Factor, **NeuroD1:** Neurogenic differentiation.

(ISPAD, 2014).