Cognitive Dysfunction in sample of Egyptian type II Diabetic Patients

Thesis

Submitted for Partial Fulfillment of Master Degree
In
Neuropsychiatry

By
Rehab Abd Ellatif Mohamed

Supervised by

Prof. Dr. Maged Mohamed Abd Elnasir

Professor of neurology
Faculty of Medicine
Cairo University

Ass. Prof. Gehan Mahmod Ramzy

Assistant Professor of neurology
Faculty of Medicine
Cairo University

Ass. Prof. Yasser Mohamed Abd Elhameed

Assistant Professor of Internal Medicine
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2013

تقرير جماعى

عن مناقشة رسالة الماجيستير الخاصه بالطبيبه / رحاب عبد اللطيف محمد توطئه للحصول على درجة الماجيستير فى الامراض العصبيه

إجتمعت لجنة المناقشه والحكم على الرساله المقدمه من الطبيبه / توطئه للحصول على الماجستير فيالامراض العصبيه والنفسيه والمشكله بقرار من مجلس الكليه والمعتمد من السيد الاستاذ الدكتور / نائب رئيس الجامعه للدراسات العليا

وتتكون من الساده الاساتذه:

أ.د. ماجد محمد عبد النصير أستاذ الامراض العصبيه بكليه الطب جامعة القاهره

(عن المشرفين)

أ.د. عصام مهدى ابراهيم أستاذ الامراض العصبيه بكليه الطب جامعةالازهر

(ممتحن خارجي)

أ.د.مها عاطف زكي أستاذدالامراض العصبيه بكليه الطب جامعةالقاهره

(ممتحن داخلي)

وذلك بمشيئة الله تعالى يوم الثلاثاء الموافق ٢٠١٣/٩/١٠ بقاعة المؤتمرات بكلية الطب (القصر العيني) جامعة القاهره قاعه (B) في تمام الساعه العاشره صباحا

الرساله مكونه من ١٤٢ صفحه باللغه الانجليزية + علاوة على ملخص باللغه العربيةيقع في صفحتين واسترشد فيها بـ ٣٣٣ مرجعا

والرساله مكونه من مقدمه وجزء نظرى مكون من ٤فصول وملخص باللغه الانجليزية واللغة العربية وقائمه بالمراجع والجزء العلمى حيث تمت الدراسه علي٢٠ مريضا يعانون من النوع ٢من مرض السكر و٢٠ من الاصحاء متوافقين في السن والنوع وتم إخضاع المجموعتين لمجموعه من الإختبارات النفسيهالي جانب الفحص الاكلينيكي واشعه مقطعيه علي المخ.

وقد اوضحت الدراسهوجود ارتباط بين مرض السكر ٢ وخلل الوظائف المعرفيه فى كلا من التعلم ، الذاكره،الفهم اللفظى و الانتباه مقارنة بمجموعة التحكم.

قررت اللجنة بعد المناقشه :

أ.د.ماجد عبد النصير أ.د. عصام مهدى أ.د. مها عاطف

I would like to start by thanking "God" for his help during this work as a little part of his generous help throughout my life.

I am greatly honored to express my deep gratitude to ***Prof. Dr. Maged Mohamed Abdel Naser****, Professor of Neurology, Faculty of Medicine, Kasr el Aini, Cairo University.*

He gave me much of his time, experience, meticulous constructive advice and support. His patience and encouragement were indispensable for completion of this work; no words would fulfill the feeling I have towards his support.

I am very proud and lucky to have ***Ass. Prof. Dr. Gehan Ramzy*** *Assistant Professor of Neurology, Faculty of Medicine, Kasr el Aini, Cairo University, supervising this work. Her valuable advises from the early beginning of this work are of great value.*

I would like to thank ***Ass. Prof. Dr. Yasser Abdel Hamed,*** *Assistant Professor of internal medicine, Faculty of Medicine, Kasr el Aini, Cairo University for his support, guidance.*

I owe lots of thanks and gratitude for all the patients and for all their families for their help.

I would like to thank all Colleagues for their support and encouragement for completion of this work.

Lastly, I would like to express my feelings of admiration, love and respect to My Parents whose support was overwhelming.

Abstract

Type 2 diabetes has been linked with increased risk of dementia and cognitive impairment among older adults and with premature mortality in young and middle-aged adults. **Objective:** This study aimed at examining the relation between type 2 diabetes mellitus and cognitive dysfunctions.**Subjects:** This study was conducted on 20 patients with type 2 diabetes of both sexes (15 males, 5 females) and twenty healthy control subjects, matched for age, sex and educational level. **Methods:** All patients were assessed using clinical evaluation, CT brain and Psychometric tests (Mini-Mental Status Examination, Beck Depression Scale, Halstead Reitan test, Wechsler Adult Intelligence Scale and Wechsler memory scale (WMS). **Results:** Statistically significant lower results were found in group1 when compared to group2 ($p<0.05$) in each of the following tests : Associative learning subtest of Wechsler Memory, Similarity and digit symbol subtests of Wechsler Adult Intelligence Scale. The results of group1 in vocabulary subtest of Wechsler Adult Intelligence Scale were lower than those of group2. However, this difference did not reach statistical significance ($P>0.05$). **Conclusions:** T2DM is a risk factor for cognitive impairment as it affects learning, memory, verbal comprehension, sustained attention and psychomotor speed.

Key words: Type 2Diabetes mellitus, cognitive functions, Wechsler memory scale.

List of Contents

List of Tables

List of Figures

List of Abbreviations

2hrPPG……..Two-hour postprandial glucose

AAMI …….....Age associated memory impairment

A-beta……Amyloid-beta

ACE……..Angiotensin converting enzyme

AChE ……Acetylcholine esterase

AD…… Alzheimer's disease

ADA ……. American diabetes association

AGE……. Advanced glycation end-product

AGEs……Advanced glycation end products

AMPA……..Amino-3-hydroxy-5-methyl-soxazolepropionic acid

APOE……Apolipoprotein E

APOE-ε4…….. Apolipoprotein E type 4

APP ……..Amyloid precursor protein

ARB …… Angiotensin receptor blocker

BB/Wor……. Rat models of type 1diabetes

BBZDR/Wor …….. Bio-breeding zucker diabetic rate (Rat models of type 2 diabetes)

CADASIL……Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CERAD…….Consortium to Establish a Registry in Alzheimer's disease

CHD…… Coronary heart disease

CNS ……. Central nervous system

CSF…….. Cerebrospinal fluid

CT…….....Computerized tomography

CVD…… Cerebrovascular disease

DCCT…… Diabetes control and complication trail

DHA ……docosahexaenoic acid

DLB……. Dementia with Lewy Bodies

DSM-IV-TR …… Diagnostic and Statistical Manual of Mental Disorders Fourth Revision, Text Revision

EEG…… Electroencephalograph

FDA…… Food and Drug Administration

FDG PET……. …….. Fluorodeoxyglucose-positron emission tomography

FPG……. Fasting plasma glucose

FSIQ……..... Full-scale I.Q.

**GABA ……..... ** Gama-Aminobutyric acid

GLUT4 ……Glucose transporter 4

GLUT8……... Glucose transporter 8 also known as **GLUTx1**

HbA1c ……Glycated hemoglobin

HRBNT……. Halstead Reitan Battery of neuropsychological test

IDDM……Insulin-dependent diabetes mellitus

IDE……Insulin-degrading enzyme

IL-6 ……... Interleukin-6

IQ …….. Intelligence quotient

KA ……Kainate receptors

MCI……Mild cognitive impairment

MI ……..Myocardial infarction

MMSE ……..... Mini-Mental Status Examination

MODY …….... Maturity-onset diabetes in youth

MRI ……..... Magnetic resonance brain imaging

mRNA ……Messenger ribonucleic

MRS…….. Magnetic resonance spectroscopy

NAA……..N-Acetyl aspartate

NGSP……National glycohemoglopin standardization program

NIDDM…… Noninsulin-dependent diabetes mellitus.

NIH-ADRDA……National Institutes of Health-Alzheimer’s disease and Related Disorders Association

NMDA……N-methyl-D aspartate

NMDA……N-methyl-d-aspartate

NOS……Nitric oxide by blocking enzyme synthase

PDD…….. Parkinson's disease Dementia

PET …… Positron emission tomography

PIQ …….. Performance IQ

RAGEs ……Receptors for AGE

REM sleep……. Rapid eye movement sleep

T1DM ……Type 1 diabetes mellitus

T2DM …….... Type 2 diabetes mellitus

UAE ……Urinary albumen excretion

VCD…….. Vascular cognitive disorder

VCI……Vascular cognitive impairment

VIQ……. Verbal IQ

WAIS …….... Wechsler Adult Intelligence Scale

WHO …….. World Health Organ

WMS-R …….. Wechsler memory scale revised

INTRODUCTION

Introduction

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced **(David et al., 2011).**

Diabetes mellitus is classified into four broad categories: T1DM, T2DM, gestational diabetes and "other specific types**.** The "other specific types" are a collection of a few dozen individual causes **(David et al., 2011).**

Diabetes is associated with premature mortality and is a risk factor for mild cognitive impairment and both vascular dementia **(Peila et al., 2002)** and Alzheimer's disease **(MacKnight et al., 2002, Arvanitakis et al., 2004).** Individuals with diabetes are ~1.5 times more likely to experience cognitive decline and frank dementia than individuals without diabetes (**Cukierman et al., 2005).** Diabetes is also associated with decrements in learning and memory, mental flexibility and information-processing speed (**Van den Berg et al., 2010).**

Type 2 diabetes mellitus(T2DM) adversely affects many aspects of brain health, increasing individuals' risk for cognitive deficits, cognitive impairment, Alzheimer's disease, stroke, diminished brain function, and brain atrophy **(Tiehuis et al., 2008, Sims-Robinson et al., 2010).** Known consequences of T2DM, including vascular disease, oxidative stress, deregulated glucose metabolism, formation of advanced glycation end products, and chronic inflammation, are each associated with adverse brain health **(Araki, 2009, Marioni et al., 2010).** T2DM is also associated with many other conditions that adversely influence cognition and brain function, including obesity, hypertension, dyslipidemia, and depression **(Williamson et al., 2007, Biessels et al 2009)**. How well glucose levels are managed during T2DM may also affect cognition **(Cukierman et al., 2009)**.Jointly, these factors may be expected to induce a broad-based and sustained spectrum of cognitive deficits, with much heterogeneity from individual to individual.

Decreased cognitive performance has been extensively described among individuals with T2DM, with reduced performance in verbal declarative memory and processing speed being the most consistently reported **(Awad et al., 2004)**. Type 2 diabetes mellitus (T2DM) is associated with an increased risk of dementia. There is still uncertainty on the etiology, but vascular disease is likely to play a role **(Biessels et al., 2008**). Clinically manifest atherosclerosis is associated with cognitive impairment in people with T2DM **(Manschot et al., 2007, Bruce et al., 2008).**

The mechanisms underlying these cognitive disorders are increasingly thought to involve mixed pathology, with contribution from vascular, neurodegenerative, and neurovascular processes **(Strachan, 2011**). Pathophysiological mechanisms that have been implicated include inflammation, oxidative stress, energy imbalance, protein misfolding and differences in genetic susceptibilities**.(Klein and Waxman, 2003 , Girouard and Iadecola, 2006)**.

T2DM-related cognitive changes and cerebral atrophy develop slowly over the course of years, at an average rate that is still within the range of that of normal aging (**De Bresser et al., 2010, Van den Berg et al., 2010).** Nevertheless, people with T2DM are overrepresented among those older individuals with accelerated cognitive decline **(Reijmer et al., 2010).**

AIM OF THE WORK

Aim of the Work

- To study the pattern of cognitive impairment in a sample of Egyptian patients with type 2 diabetes mellitus.
- To study the relationship between cognitive dysfunction and duration of diabetes.