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Assessment of Executive Function in Type 2 Diabetes Mellitus – A Case Control Study

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ABSTRACT
There is growing evidence that adults with type 2 Diabetes mellitus exhibit deficits in executive function. Primary purpose of this study was to assess executive function in type 2 DM patients. The age group studied was between 40-50 years and it was compared with the healthy controls. This is a cross sectional case control study, where in 50 consenting patients attending diabetology Outpatient department fulfilling the inclusion criteria were randomly chosen as cases and 50 consenting age, sex, education matched non diabetics were taken as controls. After screening with General Health Questionaire – 12 for psychiatric symptoms, Executive function was assessed with Digit Span Test, Verbal fluency test, Trail making test, Wisconsin Card Sorting Test and Stroop Test. In our study we found that here was no significant difference between diabetic and non-diabetic group in case digit span, verbal fluency, stroop test and WCST. There was a statistically significant difference between case and control group in Trail Making Test (p = 0.01). There was average difference of 8 seconds between diabetic and non- diabetics. The Stroop test showed a similar slowing in diabetics of 3 seconds but it was not statistically significant. Executive functioning in diabetics was comparable to that of control group. Though Trail making test, showed a statistical difference between diabetics and non-diabetic, it was still within the normative range for the particular age group.
Keywords: *Executive functions, Type 2 Diabetes, Stroop test, Wisconsin Card Sorting Test.*

Introduction

T2DM is a major public health problem all over the world[1]. The socio-economic cost of Type 2 diabetes mellitus is exorbitant, mainly due to number of associated problems that accompany diabetes mellitus, like micro and macro vascular diseases and their increased susceptibility for cognitive impairment[2,3].

Executive function is a primary domain of cognition that involves a broad set of cognitive abilities like attention, working memory, organ-ization, and persistence that are necessary for orchestrating complex, goal-directed activities[1]. Executive function appears to be orchestrated and mediated by frontal cortex along with its networks in cerebrum and sub-cortical regions of brain[4].

Recent studies and evolving data categorically suggest that executive dysfunction is causatively associated with poor glycemic control [2,5] i.e it is one of the major risk factor. The effect of Type 2 diabetes mellitus on executive function is associated with inherent micro-vascular disease affecting frontal sub-cortical function[1].

Executive function is a major domain of cognition that plays a pivotal role in allowing the execution of daily management tasks including exercise, blood glucose monitoring and drug intake, which are essential for glycemic control[1]. Executive Dysfunctions are implicated in decreased self care capacity, poor adherence to diabetic medication, decreased levels of autonomy and a decrease in ability to make essential decision, for instrumental activities of daily living, as well as resistance to proper medical care[1,5]

Suggested causes of hyperglycemia induced Executive dysfunction are

1. Diabetic vasculopathy,
2. hyper-lipidemia,
3. hypertension,
4. Insulin resistance
5. hyper-insulinemia
6. dysregulation of limbic-hypothalamic-adrenal pituitary axis (LHPA)
7. chronic hyperglycemia induced direct cytotoxicity on neuronal cells.
8. advanced glycation products
9. Inflammatory mediators like cytokines
10. oxidative stress
11. diabetes related depression

The purpose of this study is to assess executive function in patients with type 2 Diabetes mellitus in comparison to normal subjects.

Aim

To assess executive functioning in type 2 diabetic patients compared to normal subjects

NULL HYPOTHESIS There is no difference in performance, of the study and control groups, in tests of executive function.

Ethics Committee

The study was approved by the Institutional Ethical Committee, Madras Medical College.

All subjects (both patients and control group) gave informed consent for participation in written form.

Materials and Methods

Subject Selection

50 patients with type II DM attending Diabetalogy OPD in RGGGH

50 normal subjects (attenders of patients attending the OPD)

Inclusion Criteria: Age 40 – 50 years

Type II DM diagnosed as per American Diabetes Association Criteria

Age & gender matched Non Diabetics

Cooperative for Cognitive Assessment

Exclusion Criteria:

Intellectual Disabilities

Co-Morbid Medical illness

Psychiatric illness

Neurological illness

H/o of substance dependence

Assessments of Parameters:

Proforma for socio demographic data of study cases and control group

Proforma for Diabetes Status

GHQ and HAM D

Mini Mental State Examination (MMSE)

Test for Executive Function:

Digit Span Test

Forward Digit span

Reverse digit span

Verbal fluency

Letter fluency

Category Fluency

Trail making test

TMTA

TMTB

Wisconsin Card Sorting Test

Stroop Test

1. Digit Span Test

In digit span test the subject is instructed to repeat a series of numbers in the same order as said to

them. The evaluator continues to keep on increasing the series of numericals in order of one every time and then asking the subject to repeat them back to the evaluator as a long as the answers are correct and stops when a response is incorrect. Similarly in the backward digit span task the participant needs to reverse the order of the numbers.

2. Verbal Fluency Test

The Verbal Fluency battery includes tests for Letter and Category fluency. In Verbal fluency test the subject is evaluated for maximum number of word production , within a set time frame, and within a specific constraint, In the Letter Fluency test, the subject is give three separate one-minute trials for the letters F, A, and S. The Category Fluency test is a one-minute trial for a single category like birds which can fly, four legged animals etc. For Subjects not proficient English, 3 letter of their Vernacular language is given.

3. Wisconsin card sorting test

It consists of sixty four tests cards and 4 stimulus cards. Each card is a square of dimensions 8cms by 8cms. The stimuli vary in 3 attributes: color(red, green, yellow, blue), form(triangle, star, cross, circle) and number(1,2,3,4).

4. Stroop test

This test measures the response inhibition ability. Three cards which has 20 rows and 5 columns of either color names or symbol is presented. First card has color names printed in black color, second card has x symbol printed in different colors. And last card has color names blue, green, and red printed in different colors. The time taken to read each card (t1, t2, t3) and the number of errors made isnoted. The Stroop effect is calculated as: t3-(t1+t2 / 2).

5. Trail making test

Trail Making Test has two parts A and B. Each part consists of 25circles distributed over a sheet of paper. Time taken to complete the trail is noted.

Data Analysis

Statistical Analysis Plan

Comparison of socio demographic data of study and control groups:

Chi square test

Comparison of executive function of study and control groups:

Assessing normality of data for cases and controls

Shapiro-Wilk test.

Kolmogorov-Smirnov test.

Comparison of neuropsychological scores between cases (study group) and controls.

When data distributed Normally

2 Tailed Students T test

For Non-Normative distribution of data

Wilcoxon –Mann-Whitney U test (non-parametric test).

Results

The study is a case control study, cases defined as Type2 Diabetes mellitus and controls as healthy unrelated subjects.

A. Socio-demographic data of cases and controls

With respect to study population (cases), mean age was 45.14±1.5. Sex distribution was also equal among cases, 25 males and 25 females.

With respect to control group), mean age was 44.98±1.52 Sex distribution among control was 26 (52%) male and 24 (48%) female.

Comparison of socio-demographic data of cases and controls shows no significant difference. Hence the two groups are comparable with respect to age, sex distribution, education, occupation, socioeconomic status.

Table 1 : Socio-Demographic Data

Sociodemographicdata	Cases(n=50)		Controls(n=50)		$\chi 2$
	Number	Percent	Number	Percent	
Age 40 – 45 46 – 50	 26 24	 52 48	 28 22	 56 44	0.812
Sex : Male Female	 21 29	 42 58	 24 26	 48 52	0.843
Education : Secondary Degree	 37 13	 74 26	 36 14	 72 28	0.824
Occupation: Unskilled Semiskilled Skilled	 31 19 0	 62 38 0	 28 20 2	 56 40 4	0.458
Marital status : Married	50	100	50	100	
Domicile: Rural Urban	 11 39	 22 78	 12 38	 24 76	0.814
SES: Low Middle	6 44	12 88	5 45	10 90	0.769
Religion: Hinduism Christianity Islam	40 7 3	80 14 6	37 9 4	74 18 8	0.504

b. Illness characteristics of Diabetes Mellitus patients

The table2 below shows the details regarding the illness characteristics of Diabetes Mellitus patients.

Table 2: Illness characteristics of Diabetes Mellitus patients

Disease Characteristics	VARIABLES				
Age Of Onset In Yrs	<30	30 – 35	36 – 40	41 – 45	46 – 50
No. Of Patients	2	4	8	30	6
Percentage	4%	8%	16%	60%	12%
Duration Of Illness	0 -12 months	12 – 24 month	24 – 36 months	3 – 5 yrs	>5 yrs
No. Of Patients	2	6	12	20	10
Percentage	4%	12%	24%	40%	20%
Type Of Trearment	Diet / Exer	D&E + OHA	D&E + OHA + Insuin	D&E +I	
No. Of Patients	0	40	10	0	
Percentage	0	80%	20%	0	
Presence Of Complications	NEGATIVE				

The mean age of onset of diabetes mellitus is 41.40 years and the mean duration of illness is < 5 years. There was no major macro / micro vascular complication.

c. Assessment of normal distribution of data

Shapiro-Wilk and Kolmogorov-Smirnov test is used to assess the normal distribution of data.

Table 3 : Assessing normality of data for cases and controls

Tests of Normality							
CASE_CONT		Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig	Statistic	Df	Sig
STROOP TEST	CASE	0.61	50	0.15	0.950	50	0.114
	CONTROL	0.07	50	0.027	0.904	50	0.002
WCST ERRORS	CASE	0.30	50	0.15	0.962	50	0.229
	CONTROL	0.01	50	0.01	0.887	50	0.001
WCST PRE	CASE	0.03	50	0.01	0.881	50	0.001
	CONTROL	0.01	50	0.01	0.810	50	0.001

d. Comparison of neuropsychological scores between cases (study group) and controls

A total of 5 neuropsychological tests (Digit span (forward, backward), Verbal Fluency(Letter and Category Fluency), Trail making test – A&B, Stroop test, and Wisconsin card sorting test, were administered to cases and controls, yielding 17 score (Table 4& 5). Higher the scores better the performance, lower the scores, poorer the performance for Digit Span and Verbal Fluency. For trail making test the time taken to complete is scored in seconds. Higher the score poorer the performance. For Stroop test, Stroop effect is calculated, higher the score poorer the performance. The standard scores from Wisconsin card sorting test manual are entered for each parameter. Higher the score better the performance.

The Wilcoxon – Mann-whitney U test (non parametric test) is used for comparison of neuropsychological test scores of cases and controls.

Table 4: comparison of neuropsychological scores

FORWARD DIGIT SPAN					
TESTS	CAES (n=50)		CONTROLS (n=50)		SIGNIFICANT 2 TAILED P value
	MEAN	SD	MEAN	SD	
Forward digit span	6.44	0.88	6.64	1.06	0.309
Backward digit span	4.36	0.53	4.52	0.68	0.19
Letter Fluency test	41.58	3.54	42.22	2.77	0.317
Category Fluency test	13.16	1.17	13.48	1.09	0.16
TMTA	32.14	3.66	30.16	3.79	0.009
TMTB	79.68	14.81	71.18	10.03	0.002*
Stroop	42.78	7.20	40.12	8.26	0.089

TMT A & B : Trail making test A & B

For Forward Digit span test and Backward Digit span test, cases group reproduced less Numbers compared to controls and the test scores are statistically not significant.

In Letter Fluency test and category fluency test cases group produced less words compared to controls and the test scores are statistically not significant.

Trail making test A tests the speed of a subject. In this, cases took longer time to complete the task when compared to the control group and the test scores are not statistically significant.

Trail making test B tests the set-shifting ability of a subject. In this, cases took longer time to complete the task when compared to the control group. And the test scores are statistically significant at p – 0.002

Stroop test is used to test the response inhibition of executive functioning. It scores the time taken tocomplete each card and the number of errors made in each. The Stroop effect calculated using the time factor, shows cases took more time to complete the task compared to the control group . Though the errors were not used in computation of Stroop effect, cases made more errors compared to the controls in all 3 cards. the difference in their performance was not statistically significant.

Wisconsin card sorting test

Wisconsin card sorting test (WCST) is the gold standard test for executive function testing. The raw scores for each parameter were noted and their corresponding standard scores entered from test manual. The overall performance was marginally better in control group compared to cases who made more number of errors (total and perseverative) and perseverative responses. So the standardized scores were marginally low in cases compared to controls.

Wisconsin card sorting test

The tests did not show statistically significance difference between the two groups.

Table 5: Wisconsin card sorting test

W Errors								
Tests	Cases (N=50)		Controls (N=50)		Mann whitney U	Wilcoxn W	Z	Signific Ant2 Tailed
	Mean	Sd	Mean	Sd				
Error	118.28	9.272	119	9.64	1222	2497	0.193	0.849
Wisconsin Percentage Of Errors								
Tests	Cases (N=50)		Controls (N=50)		Mann whitney U	Wilcoxn W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
Error%	111.58	10.862	112.88	11.5	1177	2452	0.503	0.617
Wisconsin Presevative Response								
Tests	Cases (N=50)		Controls(N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				

PR	128.68	16.739	130.22	15.6	1184	2459	0.455	0.652

Wisconsin Presevative Response Percentage

Tests	Cases (N=50)		Controls (N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
PR%	118.22	21.539	121.1	20.8	1139	2414	0.765	0.447

Wisconsin Presevative Errors

Tests	Cases (N=50)		Controls (N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
PE	128.86	15.616	130.12	14.7	1202	2477	0.331	0.741

Wisconsin Presevative Error Percentage

Tests	Cases (N=50)		Controls (N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
PE%	118.04	19.665	119.54	18.7	1190.5	2465.5	0.41	0.681

Wisconsin Non-Presevative Errors

Tests	Cases (N=50)		Controls (N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
NPE	116	11.96	115.42	10.13	1237	2512	-0	0.928

Wisconsin Non-Presevative Error Percentage

Tests	Cases (N=50)		Controls (N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
NPE%	111	11.829	109.92	11	1212	2487	-0.262	0.794
Tests	Cases (N=50)		Controls (N=50)		Mann Whitney U	Wilcoxon W	Z	Significant 2 Tailed
	Mean	Sd	Mean	Sd				
CLR	50.5	5.559	1141	2416	0.751	0.453	0.751	0.453
CLR%	110	12.005	1209	2484	0.283	0.779	0.283	0.779
CC	5.08	0.695	1194	2469	0.386	0.703	0.386	0.703

All the test were not statistically significant.

Discussion

In our study age group selected was between 40 to 50 years. This was mainly taken to avoid any age related cognitive deficits. Formal education of at least 8th standard was applied so that the subjects could understand the tests and perform.

The digit span test did not show much difference between case and control group. The verbal fluency was also within normal limits in diabetics compared to the non-diabetics. The Wisconsin card sorting test – (WCST) (perseveration), B: WCST (category) and C: WCST (conceptual responses) also did not vary significantly between diabetics group and non-diabetics. The deficits in executive function were observed in some studies[7,8,9,10] – (Award et al., 2004; Messier, 2005; Rayn & Geckle, 2000; Stewart & Liolitsa, 1999).

Nilsson (2006)[11] suggested not all aspects of cognition may be equally or coincidentally affected by Type 2 diabetes, at least in relatively mild to-moderate cases. Executive Dysfunction could be attributed to diabetes mellitus severity its neurological sequelae or due to other associated multiple co-morbid conditions.

In our study there was a significant difference between case and control group in Trail Making Test, but it was still within the normative range for the particular age group. There was average difference of 8 seconds between diabetic and non-diabetics. The stroop test showed a similar slowing in diabetics of 3 seconds but not statistically significant. In diabetics it was observed that there was slowing in a number of speed based tasks in many previous studies. Those evaluating basic reaction time or perceptual speed were the most affected[7,8,12.13,14]. (Arvanitakis, etal 2006; Awad etal., 2004 Fontbonne, etal 2001; Messier in 2005).

Prospective multi centric and multi-national studies like LADIS[15] or randomized studies such as PROSPER[16] highlighted diabetes as an independent risk factor for cognitive impairment

in elderly individuals over 70 years. Our study group was between 40 – 50 years age group, with a duration of disease less than or equal to five years, without any vascular complications. This study group didn't show a significant executive dysfunction compared to previous studies probably due to relatively recent onset disease and a younger population group. In elderly patients, co-morbidities are higher namely hypertension, cardio-vascular, cerebro-vascular disease, psychiatric affections and drug usage. These lead to exacerbation of the executive dysfunction in them.

Conclusion

Executive functioning in patients with Type 2 diabetes mellitus was comparable to that of control group. Though Trail making test, showed a statistical difference between the diabetic and non-diabetic, it was still within the normative range for the particular age group. Validation of this conclusion requires a larger group and prospective longitudinal study. Future follow up is essential to see how the cognitive dysfunction develop in these patients over a period of time and whether they would also develop problems in their executive functions and information processing abilities as seen in other studies.

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