Executive Function Impairment in Correlation with EEG Finding in Children with Type 1 DM at School Age

Wesam E. Affia [1], Ashraf Shaheen [1], Asmaa S.M. Said [2], Basma Adel E. Abo Elasaad [3] * and Hanaa Ramadan Omar [1]

1 Pediatrics Department, Faculty of Medicine Benha University, Benha, Egypt
2 Psychiatry Department, Faculty of Medicine Benha University, Benha, Egypt
3 Public Health Ministry, Qutor Hospital و Gharbia Governorate, Egypt.
*Corresponding author: Basma Adel E. Abo Elasaad, Email: badel5634@gmail.com, Phone: +201119977616

ABSTRACT

Background: The age of onset is an important characteristic of type 1 diabetes mellitus, influencing cognitive functions. Typically, earlier onset is associated with poorer cognitive performance.

Objective: This study aimed to investigate the relationship between type 1 diabetes mellitus and cognitive dysfunction.

Methods: This study included 100 children with type 1 diabetes mellitus (DM) and 20 apparently healthy children. They were divided as follows: The patient group (Group I) comprised 100 children with type 1 DM and the control group (Group II) consisted of twenty apparently healthy children. All participants underwent a comprehensive assessment including history-taking, sociodemographic data collection, general and local examination, and laboratory investigations. **Results:** A statistically significant association was found between "start the task" function and gender, with significantly higher mean scores observed in females ($p = 0.003$). Participants' weight and height showed statistically significant negative correlations with the "organized" function ($p = 0.043$ and 0.009, respectively). Moreover, the scores of "Block response" and "Working memory" were found to exhibit statistically significant positive correlations with TLC, RBCs, and Hb levels, while they showed significant negative correlations with HbA1c levels ($p < 0.05$). **Conclusions:** Children with type 1 diabetes mellitus demonstrated notable impairments in various executive functions, indicating a potential association between glycemic control, EEG findings, and cognitive dysfunction. Monitoring cognitive function alongside medical parameters could be crucial in managing type 1 diabetes mellitus in children.

Keywords: Executive function impairment, EEG finding, Children, Type 1 DM, School age.

INTRODUCTION

Type 1 DM is a major subtype of diabetes, once known as juvenile diabetes or insulin dependent diabetes, is a chronic condition in which the pancreas produce little or no insulin. Different factors, including genetics and some viruses, may contribute to type 1 diabetes. Type 1 diabetes mellitus account for about 5% of all diabetic cases and the main feature is insulin deficiency and the patients treated with different types of exogenous insulin (rapid, short, intermediate and long-acting insulin). Thus it is called insulin-dependent diabetes mellitus [1].

Compared with non-diabetic controls, patient with type 1 DM will typically have reduced effectiveness in the following cognitive area: Intelligence, psychomotor efficiency, information processing speed, visual and constant attention, cognitive flexibility and visual perception. In some patient cognitive dysfunction was characterized by slowing mental speed and flexibility but hearing and memory were spared [2].

The age at onset is important characteristic of type 1 for influencing cognitive functions. A worse cognitive performance is usually associated with earlier age at onset. Example: hearing and memory skills are more affected in pediatric type 1 DM patient with early onset than those with late onset. Pathologically, more atrophic cerebral structural changes are found in early onset than in late onset. Chronic hyperglycemia is shown to be associated with low executive function and memory, slow fine motor speed and low receptive language functions [3]. Hypoglycemia is associated with impaired attention, flexibility, spatial ability and speed of information processing. Early visual information and contrast sensitivity are also impaired. In addition, psychomotor speed and reaction speed [4]. Diabetic ketoacidosis (DKA) is a very serious complication. Type 1 DM with DKA performs worse on spatial response task [5].

This work aimed to study the relationship between type 1 DM and cognitive dysfunction.

PATIENTS AND METHODS

Study Design and patients: This study was conducted at the Faculty of Medicine, Benha University Hospital. 100 children with type 1 DM patients for this study were recruited from the Pediatric Endocrinology Unit and Clinic of Benha University Hospitals and Tanta University Hospital. 20 apparently healthy control children were selected from Outpatient Clinic. The study was conducted through the period from February 2023 to July 2023. The children were divided into two groups: Patient group (Group I): 100 children with type 1 diabetes and control group (Group II): twenty children apparently healthy. Current study included both sexes children diagnosed with type 1 diabetes mellitus at age range from 6 to 18 years who were on conservative therapy, while children below 6 years or above 18 years, with acute or chronic infections and psychiatric or neurological diseases were excluded. **All the patients were subjected to:** Full history taking including the onset of diagnosis of type 1 diabetes mellitus, sociodemographic data, general and local examination, and laboratory investigations.

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Sociodemographic data: Age ranged from 6 to 18 years both males and females. Complications, educational progress, and diabetic coma all were recorded. The complications of diabetes mellitus can be divided into acute and chronic. Acute complication includes diabetic ketoacidosis, non-kenotic hyperosmolar syndrome and hypoglycemia. Chronic complications are related to long – term effect of hyperglycemia on vasculature and can be divided into microvascular retinopathy, nephropathy and macrovascular disease [6].

Educational progress: Children with type 1 DM found to have lower mean grades than other non-diabetic children. Diabetic coma children are alive but cannot respond to sight, sounds or other types of stimulation. Left untreated, diabetic coma can be fatal.

Psychometric investigation: Using **e**xecutive skills questionnaire [7]. It measures executive skills: Response inhibition, task inhibition, emotional control, mission start, sustained attention, planning prioritization, organization, time management, flexibility, metacognition, goal-directed persistence and stress tolerance.

Ethical considerations: The study was done after being accepted by The Research Ethics Committee, Benha University. All parents or guardians provided written informed consents prior to the enrolment of their children. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis: The collected data were recorded, and subsequent processing was carried out using the Statistical Package for the Social Sciences (IBM Corp. 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Mean ± standard deviation, median, standard error (±SE), and range were used for numerical data. Frequency and percentage were used for non-numerical data. Chi-Square test was used to examine the relationship between two qualitative variables. Correlation analysis used to assess the strength of association between two quantitative variables. All statistical tests employed a two-sided approach, and the level of significance considered for this study was set at $p \leq 0.05$.

RESULTS

No statistically significant difference was detected between the two groups regarding age, sex distribution, anthropometric data, parents with Type 2 DM history, TLC, platelets, log (Absolut amplitude Alpha-theta, µV), CF alpha, CF theta, and CF alpha-theta. Parents with type 1 DM history and sibling with type 1 DM history were higher percentage of parents with type 1 DM in the patient's group (26%) compared to the control group (5%), with statistically significant difference (p=0.04, 0.041respectively). The RBCs count, and Hb were statistically lower in patients compared to control (p=0.032). The random blood glucose (RBG), HbA1c, the log (Absolut amplitude Alpha, µV), the log (Absolut amplitude Theta, µV) were statistically higher in patients compared to control (p<0.05) (Table 1).

Table (1): Participants' demographic, anthropometric, clinical data, laboratory data and EEG assessment data

	Patients group (n=100)	**Control group (n=20)**	**p-value**
Age in years	11.1 ± 2.24	11.2 ± 2.82	0.902
Gender, n (%)			
Female	46 (46%)	9 (45%)	0.935
Male	54 (54%)	11 (55%)	
Anthropometric data			
Weight (Kg)	49.93 ± 11.3	47 ± 9.1	0.278
Height (cm)	154.6 ± 11.8	151.4 ± 11.5	0.261
BMI (kg/m^2)	21.1 ± 4.02	20.7 ± 4.07	0.752
BMI percentile (%)	72.6 ± 25.41	69.2 ± 32.95	0.599
Clinical data			
Age of onset in years	4.3 ± 1.94	--	--
Parents with Type 1 DM history	26 (26%)	1 (5%)	0.04*
Parents with Type 2 DM history	18 (18%)	3 (15%)	0.747
Sibling with Type 1 DM history	18 (18%)	0 (0%)	0.041*
Previous attacks of severe hypoglycemia	28 (28%)	--	--
Previous DKA history	63 (63%)	--	--
Laboratory data			
TLC (10^12/L)	8.04 ± 1.49	7.565 ± 1.92	0.223
Platelets (10^9/L)	271.96 ± 54.74	282.58 ± 44.65	0.409
RBCs (10^12/L)	4.93 ± 0.2	5.04 ± 0.24	0.032*
Hb (g/dl)	11.52 ± 0.77	12.71 ± 0.73	<0.001*
RBG (mg/dl)	159.68 ± 5.79	83.54 ± 10.62	<0.001*
HbA1c	7.87 ± 1.09	5.22 ± 0.25	<0.001*
EEG assessment data			
log (Absolut amplitude Alpha, µV)	1.91 ± 0.167	1.82 ± 0.23	0.036*
Log (Absolut amplitude Theta, µV)	1.73 ± 0.18	1.44 ± 0.16	<0.001*
log (Absolut amplitude Alpha-theta, µV)	2.61 ± 0.16	2.6 ± 0.13	0.896
CF Alpha (Hz)	10.1 ± 0.07	10.09 ± 0.07	0.461
CF Theta (Hz)	5.97 ± 0.12	5.98 ± 0.08	0.866
CF Alpha-Theta (Hz)	8.39 ± 0.16	8.46 ± 0.14	0.072

Data are represented as Mean + SD or frequency (%), *: significant P value.

The patients with diabetes had significantly lower block response, working memory and emotional control (Table 2).

Table (2): The participants' block response, working memory, and emotional control based on the executive functions test

		Patients group (n=100)	Control group (n=20)	p-value
Item 1	2	3 (3%)	0 (0%)	<0.001*
	4	37 (37%)	1 (5%)	
	5	41 (41%)	10 (50%)	
	6	17 (17%)	5 (25%)	
	7	2 (2%)	2 (20%)	
Item 2	2	6 (6%)	0 (0%)	0.04*
	4	26 (26%)	2 (10%)	
	5	40 (40%)	8 (40%)	
	6	19 (19%)	8 (40%)	
	7	9 (9%)	2 (10%)	
Item 3	2	3 (3%)	0 (0%)	0.007*
	4	35 (35%)	1 (5%)	
	5	39 (39%)	10 (50%)	
	6	15 (15%)	6 (30%)	
	7	8 (8%)	3 (15%)	
	Block response score	14.55 ± 1.82	16.65 ± 1.35	<0.001*
Working memory				
Item 4	2	2 (2%)	1 (5%)	<0.001*
	3	10 (10%)	0 (0%)	
	4	71 (71%)	5 (25%)	
	5	16 (16%)	12 (60%)	
	6	1 (1%)	2 (10%)	
Item 5	2	3 (3%)	0 (0%)	<0.001*
	3	6 (6%)	1 (5%)	
	4	61 (61%)	3 (15%)	
	5	29 (29%)	11 (55%)	
	6	0 (0%)	3 (15%)	
	7	1 (1%)	2 (10%)	
Item 6	2	1 (1%)	0 (0%)	<0.001*
	3	2 (2%)	0 (0%)	
	4	71 (71%)	4 (20%)	
	5	21 (21%)	16 (80%)	
	6	4 (4%)	0 (0%)	
	7	1 (1%)	0 (0%)	
Working memory score		12.52 ± 1.12	14.6 ± 1.35	<0.001*
Emotional control				
Item 7	3	14 (14%)	1 (5%)	<0.001*
	4	67 (67%)	5 (25%)	
	5	15 (15%)	11 (55%)	
	6	3 (3%)	2 (10%)	
	7	1 (1%)	1 (5%)	
Item 8	2	1 (1%)	0 (0%)	<0.001*
	3	13 (13%)	0 (0%)	
	4	57 (57%)	4 (20%)	
	5	21 (21%)	11 (55%)	
	6	5 (5%)	5 (25%)	
	7	3 (3%)	0 (0%)	
Item 9	3	1 (1%)	1 (5%)	<0.001*
	4	80 (80%)	6 (30%)	
	5	17 (17%)	12 (60%)	
	6	2 (2%)	0 (0%)	
	7	0 (0%)	1 (5%)	
Emotional control score		12.55 ± 1.26	14.6 ± 1.5	<0.001*

Data are represented as Mean + SD or frequency (%), *: significant P value.

The patients with diabetes had significantly lower ability to start the task, constant attention and planning time (Table 3).

Table 3: The participants' start the task, constant attention, and planning time based on the executive functions test

	Patients group (n=100)	Control group (n=20)	p-value
Item 10			
2	1(1%)	0 (0%)	<0.001*
3	5 (5%)	1 (5%)	
4	67 (67%)	3 (15%)	
5	17 (17%)	12 (60%)	
6	9 (9%)	4 (20%)	
7	1 (1%)	0 (0%)	
Item 11			
3	11 (11%)	2 (10%)	<0.001*
4	55 (57%)	2 (10%)	
5	33 (33%)	11 (55%)	
6	1 (1%)	4 (20%)	
Item 12			
3	6(6%)	3 (15%)	0.005*
4	65 (65%)	4 (20%)	
5	22 (22%)	11 (55%)	
6	6 (6%)	2 (10%)	
7	1 (1%)	0 (0%)	
Start the task score	12.86 ± 1.23	14.45 ± 1.36	<0.001*
Constant attention			
Item 13			
2	2 (2%)	0 (0%)	0.014*
3	9 (9%)	1 (5%)	
4	55 (55%)	4 (20%)	
5	26 (26%)	9 (45%)	
6	7 (7%)	5 (25%)	
7	1 (1%)	1 (5%)	
Item 14			
3	8 (8%)	1 (5%)	<0.001*
4	51 (51%)	5 (25%)	
5	31 (31%)	9 (45%)	
6	9 (9%)	4 (20%)	
7	1 (1%)	1 (5%)	
Item 15			
3	1 (1%)	0 (0%)	<0.001*
4	67 (67%)	3 (15%)	
5	27 (27%)	12 (60%)	
6	4 (4%)	4 (20%)	
7	1 (1%)	1 (5%)	
Constant attention score	13.11 ± 1.29	15.15 ± 0.93	<0.001*
Planning time			
Item 16			
2	1(1%)	0 (0%)	<0.001*
3	3 (3%)	0 (0%)	
4	70 (70%)	5 (25%)	
5	19 (19%)	9 (45%)	
6	6 (6%)	3 (15%)	
7	1 (1%)	3 (15%)	

	Patients group (n=100)	Control group (n=20)	p-value
Item 17			
2	1 (1%)	0 (0%)	0.008*
3	8 (8%)	0 (0%)	
4	50 (50%)	2 (10%)	
5	32 (32%)	10 (50%)	
6	9 (9%)	0 (0%)	
7	0 (0%)	2 (10%)	
Item 18			
3	4 (4%)	0 (0%)	<0.001*
4	60 (60%)	3 (15%)	
5	27 (27%)	14 (70%)	
6	8 (8%)	2 (10%)	
7	1 (1%)	1 (5%)	
Planning time score	13.11 ± 1.21	15.05 ± 1.64	<0.001*

Data are represented as Mean + SD or frequency (%), *: significant P value.

The patients with diabetes had significantly lower organization, management and flexibility (Table 4).

Table 4: The participants' organization, management, based on the Executive Functions Test

	Patients group (n=100)	Control group (n=20)	p-value
Item 19			
2	1(1%)	0 (0%)	<0.001*
3	8 (8%)	1 (5%)	
4	60 (60%)	2 (10%)	
5	23 (23%)	13 (65%)	
6	5 (5%)	3 (15%)	
7	3 (3%)	1 (5%)	
Item 20			
2	2 (2%)	0 (0%)	<0.001*
3	14 (14%)	2 (10%)	
4	53 (53%)	2 (10%)	
5	24 (24%)	10 (50%)	
6	5 (5%)	3 (15%)	
7	2 (2%)	3 (15%)	
Item 21			
2	1(1%)	0 (0%)	<0.001*
3	10 (10%)	0 (0%)	
4	71 (71%)	1 (5%)	
5	15 (15%)	16 (80%)	
6	2 (2%)	2 (10%)	
7	1 (1%)	1 (5%)	
Organized score	12.64 ± 1.291	15.35 ± 1.461	<0.001*
Management			
Item 22			
2	2 (2%)	0 (0%)	<0.001*
3	8 (8%)	0 (0%)	
4	60 (60%)	3 (15%)	
5	19 (19%)	11 (55%)	
6	7 (7%)	5 (25%)	
7	4 (4%)	1 (5%)	
Item 23			
2	5 (5%)	0 (0%)	<0.001*
3	12 (12%)	1 (5%)	
4	47 (47%)	1 (5%)	
5	11 (11%)	11 (55%)	
6	24 (24%)	4 (20%)	
7	1 (1%)	3 (15%)	
Item 24			
2	1 (1%)	0 (0%)	<0.001*
3	5 (5%)	1 (5%)	
4	65 (65%)	1 (5%)	
5	18 (18%)	12 (60%)	
6	10 (10%)	5 (25%)	
7	1 (1%)	1 (5%)	
Management score	13.57 ± 5.26	15.75 ± 1.33	<0.001*
Flexibility			
Item 25			
2	5 (5%)	0 (0%)	0.007*
3	7 (7%)	1 (5%)	
4	49 (49%)	2 (10%)	
5	25 (25%)	12 (60%)	
6	8 (8%)	3 (15%)	
7	6 (6%)	2 (10%)	
Item 26			
2	4 (4%)	0 (0%)	0.011*
3	7 (7%)	0 (0%)	
4	39 (39%)	2 (10%)	
5	30 (30%)	10 (50%)	
6	16 (16%)	4 (20%)	
7	4 (4%)	4 (20%)	
Item 27			
2	4 (4%)	0 (0%)	<0.001*
3	7 (7%)	0 (0%)	
4	42 (42%)	1 (5%)	
5	31 (31%)	12 (60%)	
6	10 (10%)	5 (25%)	
7	13 (13%)	3 (15%)	
Flexibility score	13.52 ± 1.84	16.15 ± 1.79	<0.001*

Data are represented as Mean + SD or frequency (%), *: significant P value.

DISCUSSION

The relationship between executive function impairment and EEG findings in children with T1DM is of particular interest. EEG is a non-invasive technique used to measure electrical brain activity and has proven valuable in understanding the neurological underpinnings of various cognitive and behavioral disorders. In children with T1DM, EEG studies have been conducted to explore potential correlations between altered brain activity and executive function deficits [8].

The present study showed that children with T1DM had significantly higher family history with T1DM, with either parents (26%) or siblings (18%) having T1DM. This is in agreement with the **Parkkola *et al.*** [9] who reported that familial clustering of type 1

diabetes is a conspicuous feature. The risk of developing type 1 diabetes is 8–15- fold higher in first-degree relatives and twofold in second-degree relatives. The proportion of children with an affected first-degree relative at the time of diagnosis is 10–12%, and after decades of follow-up, this frequency increases to 20%.

In this study, the RBCs count and Hb levels were statistically lower in patients compared to control. These findings are in agreement with the study of **Angelousi and Larger** [10] who reported that, with time, systemic consequences such as anemia may develop in children with T1DM, and that among the most common causes of anemia in the course of T1DM in children is iron deficiency.

The present study showed that the absolute amplitude values of brainwave frequencies, Alpha and Theta were significantly higher in children with T1DM compared to healthy control children. Our findings are in line with the previous meta-analysis study performed by **Gaudieri *et al.*** [11] reported that children with T1DM demonstrated lower performance than control subjects in the overall cognitive domains assessment. Lower scores were found in intelligence (crystallized and fluid), psychomotor activity and speed of information processing (psychomotor efficiency and motor speed), attention/executive function, visual motor integration, and academic achievement [11].

In the current study, we assessed the correlation between the execution function test parameters and the participants' demographic, clinical and laboratory data. We found a statistically significant association between "Start the task" function and gender, with significantly higher mean scores in females ($p = 0.003$). This finding is congruent with the studies of **Graziano *et al.*** [12] and **Perez *et al.*** [13] that reported more impaired cognitive functions in males with T1DM compared to females. The participants' weight showed statistically significant negative correlation with the "Organized" function. So far, those of obesity and insulin resistance with cognitive function have received considerable attention [14]. Family history with T1DM was found to be associated with lower "Start the task" function scores (in those with sibling having T1DM) and "Flexibility" function scores (in those with parents having T1DM). In agreement with these results, **Ornoy *et al.*** [15] and **Shehata and Eltayeb** [16] reported that family history was associated with higher rates of decline in executive functions.

Children with history of previous attacks of severe hypoglycemia showed significantly lower "Block response", "Working memory", "Constant attention", "Organized", "Flexibility", and "Stress tolerance". Our findings are similar to findings of **Gaudieri *et al.*** [11], and **Broadley *et al.*** [17].

Concerning the laboratory measurements, TLC showed a statistically positive negative correlation with "Block response" and "Working memory" scores. This is consistent with the study of **Wang *et al.*** [18] who presumed that inflammation and associated proinflammatory markers (which is reflected as leukocytosis) can induce chronic central inflammation, cause hippocampal nerve dysfunction, and accelerate the progression of cognitive dysfunction. Previous studies also showed that the risk of cognitive dysfunction is increased by prolonged hyperglycemia, significant variations in blood glucose concentration, and blood glucose spikes [19]. Our findings align with the data supporting the association between EEG changes and cognitive decline in children with T1DM [8, 20].

Several factors could be stated to be linked to these EEG changes. First, these abnormal patterns in brain wave frequencies can reflect neurological disturbances. These disturbances may affect cognitive processing, attention, and memory functions, leading to cognitive impairment. Second, fluctuations in blood glucose levels, which are common in children with T1DM, can impact the brain's electrical activity, including Alpha and Theta waves. Hypoglycemia episodes are associated with cognitive deficits and may be linked to the observed negative associations [20].

CONCLUSIONS

Children with T1DM demonstrated notable impairment in various executive functions, suggesting a potential association between glycemic control, EEG findings, and cognitive dysfunction. Monitoring cognitive function alongside medical parameters could be crucial in managing T1DM in children.

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