ORIGINAL ARTICLE

COGNITIVE FUNCTIONS IN CHILDREN WITH TYPE I DIABETES

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ABSTRACT

The aim: To assess the patterns and severity of cognitive impairment in children with type 1 diabetes as well as its association with disease onset and poor glycemic control.

Materials and methods: We assessed higher mental function and screened for psychosocial functioning in 60 children with type 1 DM and 60 age-matched control using the Modified Mini-Mental State examination and Pediatric Symptoms Checklist and its relation with age, gender, socioeconomic status, age at the onset of disease, duration of disease, HbA1c level, frequency of diabetic ketoacidosis and hypoglycemic attacks and type of treatment.

Results: Diabetic patients demonstrated a lower Modified Mini-Mental State examination score than controls (25.12±4.58 versus 30.08±2.95) with a highly significant difference. Furthermore, the mean Pediatric symptoms checklist score in patients was 39.08±8.18 which was much lower than that of controls 54.42±6.0 with a highly significant difference.

Conclusions: There is neurocognitive impairment in diabetic children compared to non-diabetics, and poor glycemic control whether hyper or hypoglycemia could affect their cognition and mental health.

KEY WORDS: Cognition, psychological score, Diabetes mellitus, neuronal changes

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INTRODUCTION

Chronic medical illnesses can affect the neurodevelopment and cognitive function of the brain leading to educational, occupational, and mental health disruption from children into adulthood, as the neural development extends from the early embryonic life through adolescence [1, 2]. One of the most common chronic illnesses that affect children is type 1 diabetes mellitus (DM), it affects around 171 million people worldwide, and this number is estimated to be doubled by 2030 [3]. The incidence of type 1 diabetes in children is about 0.1 – 57.6 per 100,000 [4]. Type 1 DM has been linked to alteration of hypothalamus-pituitary-adrenal axis regulation and serotonergic neuronal changes [5]. Although the exact pathology underlying this diabetic encephalopathy is not completely understood, chronic vascular and metabolic changes may be the cause [6]. The nature and extent of brain function and structure disruption are influenced by multiple factors, including age at which diabetes began, duration, and extent of blood sugar control as both hyper- and hypoglycemia can affect brain function, comorbid conditions like hypertension, micro-, and macrovascular complications [7, 8]. In hypoglycemia, the medial temporal region in the brain especially the hippocampus may be affected leading to learning and memory function impairment [5, 9]. While a prolonged and higher level of hyperglycemia correlated with white matter volume decrement within the parietal lobe in the pediatric age group [10]. As a consequence, children with Type 1 DM have somewhat lower cognitive performance across most cognitive domains; principally intelligence, memory, executive function, attention, and psychomotor speed [11-13]. Hypoglycemia is defined by a blood glucose level of 3 mmol/l or less, warning signs such as tremor, weakness, confusion, poor attention followed by a disturbing level of consciousness, convulsive seizures, coma, and even death can happen in extreme situations. Some diabetic patients experience hypoglycemia unawareness; a condition that resulted from recurrent episodes of hypoglycemia leading to loss of sensations and failure to experience the physiological warning signs of hypoglycemia, so measures to correct hypoglycemia are not taken leaving them at risk of having severe episodes. In addition, nocturnal hypoglycemia in these children may have an impact on the brain and cognitive functioning [14, 15]. Hyperglycemia is blood sugar level higher than 11.1 mmol/L (200 mg/dL), and 14 mmol/l or above is a level of symptoms may start. Poor regimen, non-compliance, as well as acute illness,

or any stressful condition can lead to frequent episodes of hyperglycemia. Hyperglycemia can lead to serious and devastating complications (e.g., nephropathy, neuropathy, and retinopathy,) in addition to diabetic ketoacidosis (DK), which may be complicated by cerebral edema, coma, and possibly death. 10-25% of affected children with DK experience chronic central nervous system morbidity [15-17]. It is thought that there is a continuum of brain damage in DK beyond massive cerebral edema [18]. Even in well-controlled children, there are intermittent oscillations in blood glucose levels. Therefore, it isn't unexpected that children with diabetes are at risk for neurocognitive impairments, which can be transient or chronic depending on the damaging insult [15].

THE AIM

The aim of this research is to assess the patterns and severity of cognitive impairment in children with type 1 diabetes as well as its association with disease onset and poor glycemic control.

MATERIALS AND METHODS

A case-control study was conducted on diabetic patients aged 7 to 14 years old, for 8 months period from December 1, 2021 to the end of July 2022. We studied 60 randomly selected patients with type 1 diabetes mellitus who had the disease for at least one month and matched them with the age and gender of 60 apparently healthy controls. Patients with any neurological, autoimmune, or other chronic diseases were excluded from the study. Informed consent was obtained from the parents for recruitment in the study. The local ethics committee at Mustansiriyah University approved the study with (IRB 7/2021 in November 21, 2021). The age of 7 years was chosen to make sure that the child at least passed his first grade of primary school so that he can read, write and know math, and asked about school performance that was required in the mini-mental state and Pediatric Symptoms Checklists. The control group was children not suffering from diabetes or any other significant chronic illness enrolled in the outpatient clinic in the central teaching hospital of pediatric visiting hospital for minor acute illnesses. All cases were subjected to detailed history (from the caregivers and the child) regarding the family income and number (large size family those who are more than 5) [19], age of onset and duration of diabetes, frequency of attacks of hypoglycemia and diabetics ketoacidosis, degree of glycemic control by HbA1c level, type of treatment whether conventional or multiple dose injections. Cognitive functions were assessed by using of a predesigned questionnaire form using the Modified Mini-Mental State (MMMS) examination [20] and Pediatric Symptoms Checklist (PSC) [21]. Modified Mini-Mental State Examination is a screening test for higher mental function and has been modified slightly for use in a children's outpatient clinic. The test, which takes 5 to 10 minutes to be performed, covers a range of cognitive functions including orientation, attention concentration, memory, language, and constructional skill. A pediatric symptoms checklist is a promising method for identifying children in need of psychiatric services through their pediatricians' consultation. The pediatric symptom checklist by [21] is a questionnaire that has been used in pediatric screening. The PSC is a 32- items questionnaire designed to be accomplished by parents of 4-18 years old children in pediatric outpatients' clinics. The PSC takes about 5 minutes to be done and reflects the parent's perceptions of their school-aged child's psychosocial performance. The PSC identifies dysfunctional children as likely to require further psychiatric assessment. PSC consists of 32 symptoms that caregiver's rate as "often, sometimes, or never" present in the child which is given a score of 0,1,2 respectively, then the mean score for all patients was compared to the mean score for the control group.

STATISTICAL ANALYSIS

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were shown as mean and standard deviation and analyzed with a Student`s t-test. Categorical variables were presented as numbers and percentages and analyzed with the Chi-square test. The receiver operating characteristic curve (ROC- curve) was used to evaluate the efficiency of 3MS and symptom score in the detection of cognitive dysfunction in patients with type 1 DM. Pearson's correlation test was used to explore the possible correlation of MMMS and symptoms with other variables in diabetic patients. A p-value less than 0.05 were considered to specify a statistically significant difference. This study was approved by the local ethics committee at Mustansiriyah University (IRB7/2021 on November 21, 2021). Informed consent was obtained from every participant and his or her parents before being included in the study.

RESULTS

The patient's mean age was 10.08±2.62 years. Females were more than males (65% of patients were female). In the control group, the mean age was 9.85±1.89

years with 75% of them being females. The income of more than half of the patient's family (61.67%) was fair. The family member of the majority of the patients was ≥5 members (large size family). The mean age of patients at the onset of the disease was 7.7±2.81 years; the disease duration was 3.17±2.79 years. In the majority of patients (73.33%) DKA occurred 0-2 times, while only a minority of patients (6.67%) experienced such complications 6-8 times throughout their illness. Hypoglycemia was reported to occur 0-2 times/month in 58.33% of the patients, while in 20% and 21.67%, hypoglycemia occurred 2-4 times and >4 times, respectively. There was a marked elevation in HbA1c with a mean of 10.49±2.43%. The vast majority of patients use a conventional treatment as shown in table I.

Diabetic patients demonstrated a lower MMMS score than controls (25.12±4.58 versus 30.08±2.95) with a highly significant difference. Furthermore, the mean pediatric symptoms checklist score (PSC) in patients was 39.08±8.18 which was much lower than that of controls (54.42±6.0) with a highly significant difference (table II).

Receiver operating characteristic curve was used for assessing the discriminative value of the MMMS as well as PSC scores in detection of cognitive dysfunction in children with type 1 DM. The area under the curve (AUC) for MMMS score was 0.816, 95% CI= 0.735-0.897, p<0.001. The test's sensitivity and specificity were 83% and 80%, respectively, at a cut-off value of 28.5. The AUC for PSC score was 0.937, 95% CI= 0.88-0.976, p <0.001. The test's sensitivity and specificity were 83% and 88%, respectively at a cut-off value of CALP= 47.5 (fig 1).

Pearson's correlation was used to find out the possible correlation of MMMS and Pediatric symptoms checklist score (PSC) with other continuous variables in diabetic patients. The MMMS score demonstrated a positive significant correlation with age (r= 0.286, p= 0.027), as shown in table III and fig 2.

Generally, the MMMS and PSC score had no association with gender and type of treatment. However, the MMMS score in patients with poor income was 23.61±4.47, which was lower than that of patients with fair income 26.05±4.46 with a statistically significant difference. Moreover, the MMMS score mean in patients experienced 6-8 times DKA was 22.5±2.64, which was significantly lower than that in patients with 3-5 times – 25.43±4.7 or those with 0-2 times – 29.5±4.04 with significant differences. Additionally, patients with >4 hypoglycemia/month had a mean of 32.92±5.93 for symptomatic score which was significantly lower than that of patients with 0-1 times/month – 40.5±7.49 or those with 2-4 times/month – 40.5±9.49 as shown in table IV.

Table I. Clinical and Demographic Characteristics of the patients

Variables	Value
Age, years	
Mean ± SD	10.08±2.62
Range	7-14
Gender	
Male	21(35%)
Female	39(65%)
Income	
Poor	23(38.33%)
Fair	37(61.67%)
Family size, persons	
<5	11(18.33%)
≥5	49(81.67%)
Age at onset, years	
Mean ± SD	7.7±2.81
Range	1.0-12.5
Disease duration, years	
Mean ± SD	3.17±2.79
Range	0.25-10
Diabetic ketoacidosis, No.	
0-2	44(73.33%)
3-5	12(20%)
6-8	4(6.67%)
Hypoglycemia, No./month	
0-1	35(58.33%)
2-4	12(20%)
>4	13(21.67%)
HbA1c	
Mean ± SD	10.49±2.43
Range	6.3-15.0
Type of treatment	
Conventional	56(93.33%)
MDI (multiple dialy injection)	4(6.67%)

Table II. The MMMS and PSC scores in diabetic patients and controls

Variables	Patients (n=60)	Controls (n=60)	p-value
MMMS score			
Mean ± SD	25.12±4.58	30.08±2.95	<0.001
Range	15-35	23-35	
PSC score			
Mean ± SD	39.08±8.18	54.42±6.0	<0.001
Range	22-55	42-63	

Table III. Pearson's correlation of MMMS and symptom score with other variables in patients with type 1 DM.

Variables	MMMS-score		Symptom score	
	Coefficient	p-value	Coefficient	p-value
Age	0.286	0.027	-0.152	0.247
Age at onset	0.244	0.086	-0.126	0.339
Disease duration	0.087	0.508	-0.006	0.966
HbA1c	0.039	0.769	-0.062	0.638
Family member	-0.054	0.683	-0.009	0.944

Table IV. Association of MMMS and PSC scores with gender, type of treatment and income in diabetic patients

Variables	MMMS-score	Symptom score
Gender		
Male	23.95±4.41	38.95±8.45
Female	25.74±4.61	39.15±8.15
p-value	0.150	0.928
Type of treatment		
Conventional	25.16±4.73	39.41±8.66
MDI	24.5±1.73	34.5±8.66
p-value	0.783	0.250
Income		
Poor	23.61±4.47	37.7±7.51
Fair	26.05±4.46	39.95±8.56
p-value	0.044	0.304
Family size		
<5	25.27±3.38	36.64±9.14
≥5	25.08±4.84	39.63±7.95
p-value	0.902	0.276
Diabetic ketoacidosis, No.		
0-2	29.5±4.04[a]	40.14±7.63
3-5	25.43±4.7[a]	35.08±7.28
6-8	22.5±2.64[b]	39.5±14.43
p-value	0.018	0.166
Hypoglycemia, No./month		
0-1	25.97±4.51	40.5±7.49[a]
2-4	24.5±4.91	40.5±9.49[a]
>4	23.38±4.23	32.92±5.93[b]
p-value	0.195	0.007

Note: Different small letters indicate significant difference..

DISCUSSION

In this study, the mean age of the patients was 10.08±2.62 years, which did not significantly differ from that of Eldamo A. et al., [22] in Egypt which was 11.46±3.21 years. In this study, the mean age at onset of diabetes was 7.7±2.81 years (range from 1-12.5 years) and disease duration was 3.17±2.79 years (range from 0.25-10 years). While in Eldamo A. et al., [22] the mean age of onset of diabetes-studied cases was 8.54±2.26 years (range of 4-13 years) and the duration of illness ranged from 1-8 years. Diabetic patients demonstrated a lower MMMS score with a highly significant difference than controls 25.12±4.58 versus 30.08±2.95. In agreement with Shuba N et al., [23] and Eldamo A. et al., [22] who screened the mental state of patients with type 1 diabetes through the modified mini-mental status examination, show that there was a highly significant difference between diabetic and control groups as regards to MMMS, being lower in diabetic patients. Furthermore, the mean pediatric symptoms checklist score in patients was much lower than that of controls with a highly significant difference: 39.08±8.18 versus 54.42±6.0. similar to results found by Reynolds KA et al., [24] and Eldamo A. et al., [22]: 38.96 ± 4.03 versus 50.26 ± 4.88; respectively. The area under the curve (AUC) for MMMS score was 0.816(81.6%), 95% CI= 0.735-0.897, p<0.001. The test's sensitivity and specificity were 83%, 80% respectively, at a cut-off value of 28.5 in the receiver operating characteristic (ROC) curve used to evaluate the discriminative value of the MMMS and PSC scores. The area under the curve for PSC score was 0.937 (93.7%), 95% CI= 0.88-0.976, p <0.001. The test's sensitivity and specificity were 83%, and 88% respectively at a cut-off value of CALP= 47.5, Nearly the same result s found by Eldamo A. A. et al., [22] shows that the best cut-off point for MMMS to detect cognitive dysfunction in diabetic patients was found ≤ 27 with a sensitivity of 58%, specificity of 76% and AUC of 74.4%. the best cut-off points for PSC to detect cognitive dysfunction in diabetic patients was found ≤ 42 with a sensitivity of 84%, specificity of 92%, and AUC of 96.1%. The MMMS and PSC score in patients with poor income were lower than that of patients with fair income with a significant difference in MMMs scores, this could be explained by poor access to institutional resources e.g., good schools, child care, and medical facilities. Frequent attacks of DKA were associated with more decline in cognitive function in these children in agreement with Ghetti S et al., [25] in the US who states that repeated DKA exposure was associated with lower IQ among diabetic children. Additionally, patients with >4 hypoglycemic attacks /month had a mean of 32.92±5.93 for a symptomatic score which was significantly lower than that of patients with 0-1 times/month or those with 2-4

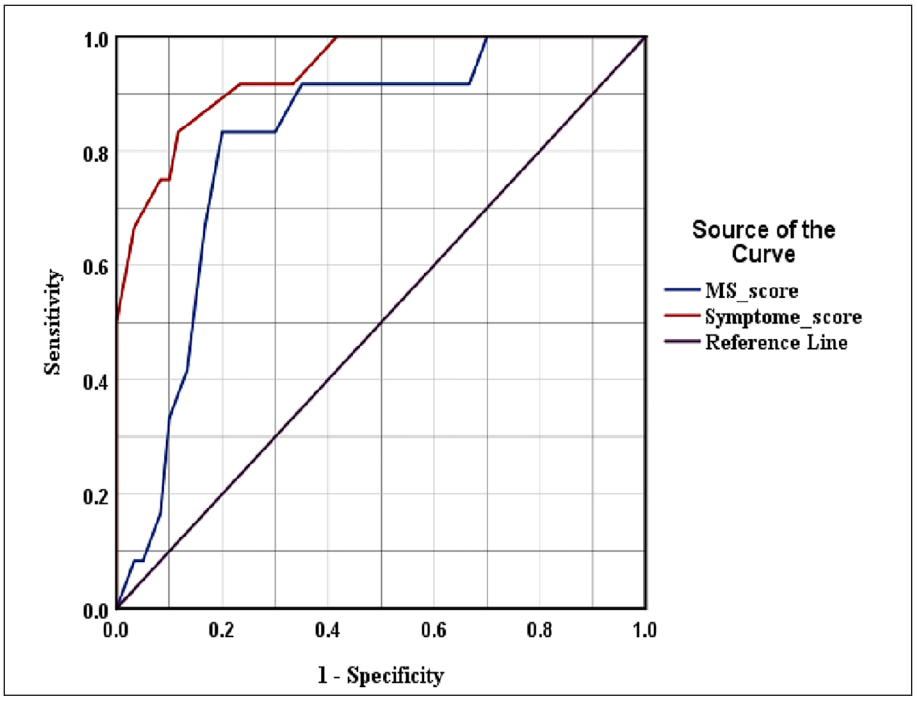

Fig. 1. Receiver operating characteristic curve of MMMS and symptom score to detect cognitive dysfunction in patients with type 1 DM

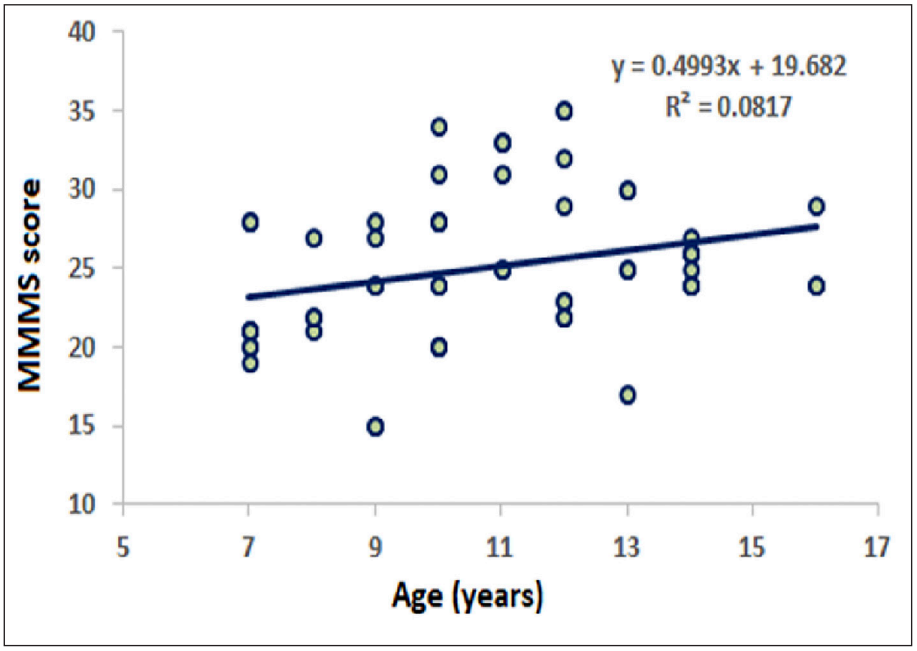

Fig. 2. Scatter plot and regression line between age and MMMS score in patients with type 1 DM

times/month results supported by Blasetti A et al., [26] who hypothesized that frequent severe hypoglycemia has a negative effect on cognitive functions of diabetic children. The MMMS score demonstrated a positive significant correlation with age but no correlation with gender, duration of the disease, level of HbA1c, and the number of family members, Shuba N Karan [23] states that diabetics patients showed significantly decreased cognition based on MMMS scores, and there was no significant correlation of age, sex, the duration of diabetes and HbA1C among the diabetics with cognitive function. Ohmann S et al., [5] in Australia found that DM type 1 is associated with cognitive dysfunction in adolescents independent of the degree of metabolic control and the disease duration. These deficits are probably related to early-onset of the disease. These variabilities could be explained by the small sample size and different socioeconomic states.

CONCLUSIONS

There is cognitive impairment in diabetic children compared to non-diabetics, and poor glycemic control whether hyper or hypoglycemia could affect their cognition and mental health, to optimize the cognitive function of these children; more efforts should be made to normalize their blood glucose level.

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The Authors declare no conflict of interest.

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