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Assessment of Cognitive Functions in Children with Type 1 Diabetes Mellitus Following Diabetic Ketoacidosis

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ABSTRACT

Background: Cognitive impairment has been linked to microvascular complications in type 1 diabetes mellitus (T1DM), with diabetic ketoacidosis (DKA) associated with memory and attention deficits, as well as brain structural changes. However, it remains unclear if a single or multiple DKA episodes lead to measurable cognitive declines shortly following the episode in kids with new-onset T1DM.

Aim: To evaluate the association between DKA episodes and cognitive deficits in kids with T1DM.

Patients and Methods: This case-control research has been carried out on sixty-four kids aged 12–15 years with T1DM at Suez Canal University Hospital. Group 1 (n=32) had no history of DKA, while Group 2 (n=32) had experienced at least one DKA episode more than one month prior to the study. This study was conducted over six months, from November 2023 to April 2024. Children with other chronic or endocrine diseases were excluded. Cognitive performance has been evaluated utilizing the Arabic versions of the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) and the basic modification of the Montreal Cognitive Assessment (MoCA-Basic). Evaluated domains included executive function/psychomotor speed, language, attention, and episodic memory.

Results: Children with a history of DKA showed significantly lower WISC scores ($p = 0.03$), indicating impaired cognitive performance. However, insignificant variances have been observed in cognitive function based on the number of DKA episodes or HbA1c levels.

Conclusion: A history of DKA in children with T1DM may negatively impact cognitive function, regardless of episode frequency or glycemic control.

Keywords: T1DM, DKA, cognitive functions.

INTRODUCTION

The global yearly frequency of type 1 diabetes mellitus is around 98,200 new cases among kids under fifteen years old [1]. Over one-third of newly diagnosed kids are affected by diabetic ketoacidosis [2].

Throughout an episode of diabetic ketoacidosis, numerous abnormal processes occur in the body, involving fluid changes, reduced perfusion, and disrupted pH, which affect numerous functions and lead to electrolyte anomalies. All of these may affect several body systems and organs [3].

The pathogenesis of brain insult in DKA isn't widely recognized. Three potential mechanisms have been suggested: vasogenic edema, osmotic edema resulting from aggressive fluid therapy, and ischemia accompanied by cytotoxic edema. It is probable that one of the pathologic mechanisms, or all three, could be operating to various levels in the affected cases [4].

Information consistently demonstrates a correlation between several measures of hyperglycemia and cognitive function in individuals having T1DM. Diabetic ketoacidosis is related to cognitive deterioration, despite the absence of overt neurological signs throughout the attack. Young kids may have increased susceptibility and a heightened probability of developing these decreases [5]. Additionally, investigations have reported a consistent correlation between the occurrence of microvascular complications and cognitive impairment with T1DM [6]. Other reports indicate that DKA is related to changes in attention, memory, and variations in brain microstructure [7].

Regardless of this proof, multiple questions remain. First, it isn't clear whether a single diabetic ketoacidosis episode leads to persisting cognitive drops that are identifiable shortly following the diabetic ketoacidosis episode in kids with new-onset T1DM. The majority of research indicating worse cognitive function following a single diabetic ketoacidosis episode were retrospective, including kids previously diagnosed having T1DM or exhibiting documented abnormalities in contrast to control subjects without a T1DM diagnosis [8,9].

This investigation aimed to evaluate the correlation between DKA episodes and the possible development of cognitive deficits, thus improving the mental health of children with T1DM.

PATIENTS AND METHODS

This was a case-control investigation that was performed on sixty-four kids diagnosed with T1DM aged from 12 to 15 years in the inpatient and outpatient units of the Pediatric Department, Suez Canal University Hospital. The cases have been separated into two demographically matching groups. Group **1 (control** group) involved 32 cases with no previous history of DKA, and Group **2 (case** group) involved 32 patients with at least one previous attack of DKA that had elapsed at least one month before enrollment in the study. Patients with known other chronic illnesses or other endocrine diseases were excluded. This study was conducted over six months, from November 2023 to April 2024.

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All patients in the study underwent history taking, including personal data, T1DM-related history, and history of previous DKA attacks. The average HbA1c level over the last two years was measured.

All the 64 participants were subjected (both orally and in writing) to a comprehensive cognitive battery by the same trained interviewer. Four cognitive domains have been recognized: language, psychomotor, episodic memory / executive function, speed, and simple attention using WISC-IV and MoCA-Basic Arabic versions.The WISC-IV is a standardized assessment consisting of 15 subtests, including 10 core and 5 supplemental/optional. This tool gives a Full-Scale Intelligence Quotient (FSIQ) along with 4 index or composite scores. Scores are presented as standard scores with a mean of 100 and a SD of 15, indicating that about two-thirds of the general population will achieve a full-scale IQ score between 85 and 115 on the WISC-IV.

The MoCA-Basic is a screening instrument developed in 2005 specifically to detect mild cognitive impairment with a sensitivity of 80% to 100% and a specificity of 50% to 76%. It is a 30-point test that assesses 6 cognitive domains: executive functioning, visual perception, language, orientation, attention, and memory. The total score on the MoCA test varies from zero to thirty. The outcomes can be interpreted as normal cognition with a score varying from 26 to 30 points, mild cognitive impairment with a score varying from 18 to 25 points, moderate cognitive impairment with a score varying from 10 to 17 points, and severe cognitive impairment with a score range of less than 10 points [10].

Statistical analysis

The data obtained has been recorded in the case sheet. Statistical analysis has been done by Statistical Package for the Social Sciences (SPSS) for Windows version 18. Quantitative data were presented as mean and standard deviation (SD) and were compared by the independent t-test. Mann-Whitney test, for abnormally distributed quantitative variables, to compare two studied groups. Qualitative data were presented as frequency and percentage and were compared by the Chi-Square test. Correlations between different study variables were done using the Pearson correlation test. linear regression analysis for prediction of WISC and MoCA cognitive scores.

A p-value of not more than 0.05 has been considered statistically significant.

Ethical approval:

All the procedures of the research have been approved by the Pediatrics Department and the Investigation Ethics Committee of the Faculty of Medicine, Suez Canal University. Administrative consents required were taken from the caregivers of the participants. This research has been performed in compliance with the Declaration of Helsinki, the code of ethics of the World Medical Association.

RESULTS

Insignificant distinctions were observed between both groups regarding demographic data (Table 1).

Table 1*:* Demographic data of the examined cases

Variables	Group 1 *(Number=32)*		Group 2 *(Number=32)*		P-value	Sig.
	Mean	SD	Mean	SD		
Age (years)	13.3	1.1	13.2	1.12	0.74	NS
Gender	**N**	**%**	**N**	**%**		
Male	17	53.1	13	40.6	0.32	NS
Female	15	46.9	19	59.4		
Residence	**N**	**%**	**N**	**%**		
Urban	8	25	4	12.5	0.20	NS
Rural	24	75	28	87.5		

There was a statistically insignificant variance between both study groups regarding the severity or the frequency of hypoglycemic attacks or the level of HbA1c (Table 2).

Table 2: Hypoglycemic attacks data and HbA1c levels of the examined cases

Variables	Group 1 *(Number=32)*		Group 2 *(Number=32)*		P-value	Sig.
Hypoglycemic attacks	**N**	**%**	**N**	**%**		
No	3	9.4	8	25	0.098	NS
Yes	29	90.6	24	75		
HbA1c	Mean	SD	Mean	SD		
	9.2	1.3	9.5	1.2	0.41	NS

HbA1c: Hemoglobin A1c

A statistically significant variance has been observed among both study groups with regard to the level of cognitive function, that measured by the total WISC-IV mean score, which was higher in the control group, reflecting a better performance (Table 3).

Table 3: Cognitive function scores in the examined patients

Variables	Group 1 *(Number=32)*		Group 2 *(Number=32)*		P-value	Sig.
	Mean	SD	Mean	SD		
Verbal Compression Index	109.1	8.7	105.2	11.2	0.13	NS
Working Memory index	93.9	11.1	92.6	12.3	0.67	NS
Perceptual Organization Index	91.6	6.9	88.6	9.7	0.16	NS
Processing Speed Index	94.2	10.7	89.7	10.8	0.09	NS
Total WISC scoring	98.5	7.5	93.8	10.3	**0.03***	S
MoCA scoring	24.9	2.8	23.7	3.3	0.25	NS

*: Significant **WISC**: Wechsler Intelligence Scale for Children, MoCA: Montreal Cognitive Assessment score.

A statistically insignificant variance has been seen in cognitive function scores, as measured by WISC-IV and MoCA, and the frequency of DKA attacks among patients in group 2 (Table 4).

Table 4: Correlation between cognitive function scores and frequency of DKA attacks in group 2

Frequency of DKA	WISC score		P-value	MoCA score		P-value
	Mean	SD		Mean	SD	
Once before	89.4	16.2	0.933	24.07	2.7	0.700
Two or more times	88.5	14.8		19.5	9.2	

DKA: Diabetic Ketoacidosis **WISC**: Wechsler Intelligence Scale for Children **MoCA:** Montreal Cognitive Assessment score.

A statistically insignificant correlation has been seen in the level of cognitive function score assessed by both WISC-IV and MoCA scores and the HbA1c level among group 2 patients (Table 5).

Table 5: Correlation between cognitive function scores and HbA1c level in group 2

Variables	HbA1c	
	r	p-value
WISC score	0.20-	0.11
MoCA score	0.23-	0.07

WISC: Wechsler Intelligence Scale for Children, **MoCA:** Montreal Cognitive Assessment score, HbA1c: Hemoglobin A1c.

There was no statistically significant prediction effect of any of the study variables on the cognitive level by WISC-IV or MoCA scores (Table 6).

Table 6: Multivariate linear regression analysis to determine the power of different variables in the prediction of WISC and MoCA cognitive scores in the examined patients

Variables	WISC Score		MoCA Score	
	t	Sig.	t	Sig.
(Constant)	2.609	0.015	2.289	0.031
Age	0.594	0.558	0.628	0.536
Age at diagnosis	1.720	0.098	0.673	0.507
Hypoglycemic attacks	0.193	0.849	0.453	0.654
Frequency of hypoglycemic attacks	0.094	0.926	-0.389	0.701
Frequency	-0.731	0.472	-1.608	0.120
HBA1c level	-0.352	0.728	-0.058	0.954

WISC: Wechsler Intelligence Scale for Children, **MoCA:** Montreal Cognitive Assessment score, HbA1c: Hemoglobin A1c.

DISCUSSION

This study stated that the control group demonstrated a statistically significant superior performance level of cognitive function that has been determined via the total WISC score. But no statistically significant association between the cognitive function scores and the frequency of DKA attacks was found.

In accordance with our findings utilizing the English version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), two to six months post-DKA episode, one study [5] observed kids who underwent DKA, irrespective of its severity, demonstrated significantly reduced IQ scores compared to those who didn't experience DKA.

Also, in agreement with our study, a study utilizing a validated Arabic version of the Stanford–Binet test found that kids with recurrent diabetic ketoacidosis performed below average in nonverbal fluid reasoning tasks regardless of their frequency among the affected children [11].

Another study using comprehensive neurocognitive assessments, including spatial memory and color tasks assessing long-term memory, found that a single diabetic ketoacidosis episode is related to subtle memory decrees quickly following type 1 diabetes diagnosis. Sizable IQ reductions are obvious in kids with identified diabetes, recommending that diabetic ketoacidosis effects might be worsened in kids with chronic exposure to hyperglycemia [12].

In a longitudinal study (baseline and monitoring testing eight to twelve weeks later), using the Mini-Mental State Examination (MMSE), Wide Range Assessment of Memory and Learning second edition (WRAML-2), Stanford-Binet, WISC-IV, and DKEFS (Delis-Kaplan Executive Functioning System), there were lower scores in visual cognitive tasks in the DKA group in comparison with the non-DKA group [13].

Prospective evaluated research conducted at baseline and eighteen months later, utilizing WPPSI-III, WASI, NEPSY-II, CPT-2, and WJ-III Cognitive CMS, revealed that at eighteen months, kids with moderate to severe DKA had reduced IQ scores and worse performance on memory tasks and attention compared to kids who had no or mild DKA [14].

In disagreement with our outcomes, population research of Danish kids didn't discover overall variances among school kids with and without diabetic ketoacidosis exposure in performance on standardized reading and mathematics test scores. The degree of DKA wasn't recorded in this population research. If diabetic ketoacidosis was predominantly avoided or managed while still mild, neurocognitive deficits might have been less probable to emerge in that sample [15].

Another large study demonstrated that moderate to severe diabetic ketoacidosis was associated with reduced IQ and poorer performance on memory tasks, but in contrast to our results, this study stated that earlier episodes of diabetic ketoacidosis and greater HbA1c were related to reduced IQ among kids who weren't newly identified [16].

The difference between researchers regarding the effect of DKA in T1DM on cognitive function may be attributed to the difference in methodology used in assessing the cognitive function and its duration, the age of the studied children, the sample size, and associated problems. Finally, the majority of previously published research utilized various cognitive evaluation methods that lack a validated Arabic version, hence complicating the comparison with our findings.

CONCLUSION

Our results lead us to hypothesize that DKA disrupted cognitive function and identified trends towards group differences are likely related to the impact of DKA on the developing brain, underscoring the significance of DKA prevention when T1DM is recognized and prompt identification of kids with new onset of T1DM, and over time, the effects become more pronounced thus more easily detected.

RECOMMENDATIONS

Knowledge enhancement programs that increase understanding and knowledge of diabetes for kids and their caregivers are strongly suggested. It is also recommended to perform cognitive function assessment for every patient suffered one or more attacks of DKA to improve their mental health. Larger longitudinal follow-upstudies are needed to further identify possible modifiable risk factors for cognitive impairment in diabetes.

LIMITATIONS

The sample size was relatively small, which might have led to the decreased impact of the results. The study was done in only one hospital, which makes it less representative of the Egyptian population. The sampling method was a convenient sampling method, which may have led to bias in case and control selection. We did not particularly examine the social or academic consequences of any cognitive deficits.

DECLARATIONS

Consent for publication: I certify that each author has granted permission for the work to be submitted.
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Competing interests: None.

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