Evaluation of Cognitive Functions in Iranian Children and Adolescents With Diabetes Mellitus

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Abstract- Diabetes in children and adolescents is a chronic condition with an expanding trend in the community. Several studies have shown cognitive dysfunctions are the most important side effects of diabetes among individuals of younger ages. Due to cultural differences and their impact on cognitive issues, the authors decided to assess the cognitive functions of Iranian children and adolescents with diabetes. Cognitive functions including memory, attention and executive functions were evaluated in 62 diabetic children and adolescents and healthy peers using CANTAB cognitive tests. Other data such as demographic, school performance and medical information were collected by questionnaires. Except in the case of few variables in RVP, SSP and SST, no significant difference exists between diabetic children and the control group in terms of different cognitive domains. But cognitive variables, especially in PRM, SWM and SOC test, has been shown to be deteriorated with increasing HbA1C values in serum levels. Diabetes has no impact on the cognitive functioning of children provided by maintaining a glycemic control. It is proposed that the adoption of appropriate parenting styles and family and social support can prevent cognitive changes in children with diabetes.

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Introduction

Diabetes in children and adolescents is a chronic condition with an expanding trend in the community. According to some studies, approximately 15 million children in the world have diabetes, and its rising prevalence is alarming in recent years (1,2). Also, some studies have suggested an increase of 5% in the early onset of diabetes in younger ages (3).

The most challenging diabetes-related problems in the ages of children and adolescents are the difficulty to control the disease and to achieve an optimal glycemic control due to some reasons such as hormonal changes during puberty, psychological problems, and mood changes during adolescence (4,5). So far, several studies have investigated the relationship between cognitive function and diabetes among adults (6), and similar studies have been conducted recently on children and adolescents with diabetes. The results of these studies have generally highlighted the negative impact of diabetes on cognitive function. However, this relationship has not been observed in some studies (7). But, those studies confessing the impact of diabetes on cognitive function have considered glycemic control as the most important factor influencing these functions (8).

Given the high rates of treatment failures in children and adolescents; however, it seems that cognitive dysfunction such as memory, attention, and executive functioning are the most important side effects of diabetes among individuals of younger ages. Due to the substantial burden of these functions on different areas

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of development such as behavioral, cognitive, developmental, and social cognitive, special attention should be paid to these psychological perspectives in diabetic children and adolescents. However, generalizing the cognitive studies conducted on children and adolescents in different countries to each other should be done with caution. Because these cognitive functions are influenced by various factors including cultural, educational, social and economic factors which should be considered in the assessments (9,10). Besides, Distinctions should be made between health care systems in different societies. Due to this condition, a heterogeneity remains in terms of glycemic control and other factors related to diabetes management including drugs and therapeutic options available for patients with diabetes in different societies, especially in children and adolescents, which affects the management of diabetes (11).

In Iran, the prevalence of diabetes in children and adolescents is growing (12). Different characteristics of the Iranian society including health care system, family structure, social protection, and other similar issues have created differences between Iran and other countries, so that each of them might affect the relationship between diabetes and cognitive functions in children and adolescents.

Having this in mind; the authors decided to assess the cognitive functions of Iranian children and adolescents with diabetes to identify the impact of glycemic control parameters on these functions.

Materials and Methods

This study is part of the ABCD study protocol which has already been published by the authors (13).

Ethical approval

The study has received the authorization code of 00 300 by the Research Ethics Committee of Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences. All samples were explained for the purpose of the study. And, given the age of the subjects, the informed consent was signed by their parents before entering into the study.

Sample collection

In order to gain access to children and adolescents with diabetes, an information bank in Endocrinology and Metabolism Research Institute was used to extract records of patients aged 6 to 12-year-old referring to the specialty clinics of the Institute. Followed by a telephone contact with the families of diabetic children and explaining the purpose of the study, they were invited to participate in the project.

The children, accompanied by their parents, attended the clinic for conducting cognitive assessment tests. After a face-to-face conversation between the researcher and the patients and their families on the study purpose and qualifying the patients for entering into the study, they were given a demographic questionnaire validated by some experts opinion and consent form for initiating the study. Inclusion criteria were: no history of chronic diseases other than diabetes, living with both parents, studying at a state-run school, no history of diagnosed central nervous system diseases, no history of medication conflicting with the cognitive processes of the nervous system, and no signs of learning disabilities detectable by the trained researchers.

Also, a number of students were randomly selected from state run schools in Tehran (location where the study conducted), and were assigned to the control group.

The process through which the controls were entered into the study was similar to that of the cases, except that the control group did have neither diabetes nor its early symptoms (i.e. bulimia, polydipsia, polyuria, nocturia, etc).

Cognitive assessment

In order to assess the cognitive domains of attention, concentration, memory, and executive functions, the computer based test of Cambridge Automated Neuropsychological Test Battery (CANTAB) with the Software key of 203618928 was used. CANTAB is language and culture free, and then is suitable for application in different countries. A description of the tests applied in CANTAB and areas evaluated by any of these tests are given in Table 1.

A well-trained researcher conducted the tests in a quiet room without the presence of parents. The testing procedure was explained to participants, and then subjects sat behind a computer for a test run. Each assessment lasted about 1 hour and depending on the subjects' perceived ability a 5 minutes rest was considered in the course of test execution.

Table 1. CANTAB tests and areas of evaluation used in the study

Test name	Purpose/ cognitive domain evaluated
Motor screening (MOT)	Visual, movement and comprehension difficulties
Intra-extra dimensional set shift (IED)	Executive functions, working memory, and planning test (assesses rule acquisition and attentional set shifting)
Pattern recognition memory (PRM)	Visual memory test (tests visual recognition memory)
Rapid visual information Processing (RVP)	Attention test (tests visual sustained attention)
Stocking of cambridge (SOC)	Executive functions, working memory, and planning test (assesses spatial planning and motor control)
Spatial span (SSP)	Executive functions, working memory, and planning test (tests working memory capacity)
Spatial working memory (SWM)	Executive functions, working memory, and planning test (assesses working memory and strategy use)
Stop signal test (SST)	Decision making and response control test (gives a measure of response inhibition)

Data analysis

Collected data regarding factors associated with diabetes and the assessment of cognitive functions were analyzed using SPSS software. We used T-test for comparing cognitive assessments in two study groups and Pearson Correlation Coefficient for evaluating correlations between cognitive and diabetes indices.

Results

In this study, 31 children and adolescents with diabetes with an average age of 10.26 years (SD=2.23) and 31 healthy children and young adults with an average age of 9.97 years (SD=1.47) were evaluated. Demographic data of samples is presented in Table 2. No significant correlation was found between the age of diabetes onset and duration of diabetes.

The mean duration of diabetes in the studied patients was 59.71 months (SD=37.06). 13 of them had a history of one or more hypoglycemic attacks during the past year. 5 patients had experienced a history of Diabetic Keto-Acidosis (DKA) attack at least once during the past year. 6 patients also reported a history of hospitalization due to diabetes and its complications in the past year. The latest HbA1C level before conducting cognitive assessment tests on participants was 8.18 (SD=1.50) encompassing the highest level as 11.5 and the lowest as being 6. Different antidiabetic regimens were reported to be used in patients depending on what prescribed by their physicians. Also, different kinds of insulin preparation were used by the patients including regular insulin, NPH, glargine, etc. One patient reported using insulin pump.

Results of Rapid Visual Information Processing (RVP) showed that the total false alarms, representing the number of occasions that participants responded outside the framework, was significantly lower in the control group than the cases which indicate a better performance of the healthy group (P=0.027) (Table 3).

Table 2. Demographic characteristics of participants

		Diabetics (N=31)	Healthy controls (N=33)	Total (N=64)
Mean age		10.26 (2.23)	9.97 (1.47)	10.11 (1.87)
sex	Male	13 (41.9%)	10 (30.5%)	25 (40%)
	female	18 (58.1%)	21(69.5%)	39 (60%)
Education in normal schools	Yes	33 (100%)	31(100%)	64(100%)
	No	0	0	0
Duration of diabetes	--	59.71 (37.06)	--	--
History of hypoglycemic attack	Yes	13	--	--
	no	20	--	--
History of diabetic Keto-Acidosis*	Yes	5	--	--
	no	28	--	--
History of hospital admission**	Yes	6	--	--
	no	27	--	--

*During the last year

**Because of diabetes or diabetic complications

Table 3. Results of CANTAB cognitive assessment in diabetics and healthy controls

Test	Measures	Diabetics			Healthy group			Sig. (2-tailed)
		Mean	Std. deviation	Std. error mean	Mean	Std. deviation	Std. error mean	
Motor screening (MOT)	Mean latency	800.558	211.8780	38.0544	867.721	312.0944	54.3287	.321
	Mean error	11.780	3.5764	.6423	10.608	2.4370	.4242	.129
Pattern Recognition Memory (PRM)	Mean correct latency	2.1880E3	879.68632	160.60801	2.2630E3	1005.11311	174.96773	.755
	Mean correct latency	2.1880E3	879.68632	160.60801	2.2630E3	1005.11311	174.96773	.755
Spatial Span (SSP)	Number of attempts (span length 2)	1.00	.000	.000	1.40	.754	.169	.028
	Span length	5.19	1.276	.229	4.50	2.115	.473	.150
Spatial Working Memory (SWM)	Between errors	50.17	15.660	2.859	56.03	18.065	3.145	.176
	Between errors (4 boxes)	3.23	3.234	.591	4.91	3.844	.669	.067
	Between errors (6 boxes)	14.80	7.703	1.406	18.09	8.175	1.423	.106
	Between errors (8 boxes)	32.13	8.468	1.546	33.03	10.318	1.796	.709
	Strategy	37.80	3.652	.667	37.70	3.746	.652	.913
	Total errors	50.90	15.832	2.890	56.30	18.285	3.183	.217
	Total errors (4 boxes)	3.30	3.196	.584	4.91	3.844	.669	.077
Stocking of Cambridge (SOC)	Mean initial thinking time (2 moves)	990.517	1111.1544	206.3362	1.015E3	1103.9083	195.1453	.932
	Mean initial thinking time (3 moves)	1672.86	1656.009	307.513	1751.31	1308.295	231.276	.837
	Mean initial thinking time (4 moves)	2.1065E3	1902.37170	353.26156	1.4226E3	1192.77420	210.85468	.095
	Mean initial thinking time (5 moves)	1.5197E3	1291.98620	239.91581	1.2124E3	1003.88602	209.32470	.353
	Mean moves (2 moves)	2.13	.346	.063	2.15	.364	.063	.840
	Mean moves (3 moves)	3.833	.8644	.1578	4.515	1.0115	.1761	.006
	Mean moves (4 moves)	5.95	1.148	.213	5.92	1.222	.213	.923
	Mean moves (5 moves)	8.09	1.673	.311	7.95	1.325	.250	.729
	Problems solved in minimum moves	6.13	1.634	.298	5.42	1.696	.295	.097
Intra-extra Dimensional Set Shift (IED)	Completed stage errors	14.32	9.569	1.719	12.48	6.722	1.207	.385
	Total errors	27.58	13.426	2.411	23.16	12.546	2.253	.186
	Total latency	1.72E5	52499.707	9429.226	1.32E5	57986.325	10414.651	.006
Choice Reaction Time (CRT)	Percent commission trials	1.04	3.455	.958	.48	1.436	.313	.512
	Percent correct trials	96.03	3.947	1.095	96.59	3.705	.809	.679
	Mean correct latency	5.6802E2	169.95055	47.13580	5.9715E2	236.06159	51.51286	.702
Stop Signal Test (SST)	Total commission errors	.30	1.259	.263	.28	.843	.169	.937
	Total omission errors	.00	.000	.000	.12	.440	.088	.197
	Direction errors on stop and go trials	3.28	2.975	.552	2.42	2.318	.455	.245
	Total correct on stop and go trials	196.00	80.265	14.905	151.23	44.873	8.800	.013
Rapid Visual Information Processing (RVP)	Mean latency	474.54	255.067	76.906	400.50	116.673	82.500	.703
	Total false alarms	1.17	2.421	.450	.10	.557	.103	.027
	Total hits	3.76	7.165	1.330	.34	1.675	.311	.018
	Total misses	12.07	12.145	2.255	.55	2.971	.552	.000

Also, the total hits, representing the number of occasions the participant responded correctly to a target sequence within the response window, was significantly higher in patients with diabetes than the controls which indicate a better performance of cases (P=0.018). Another variable, the total misses, representing the number of occasions the participant failed to respond to a target sequence within the response window was significantly lower in healthy individuals compared to those with diabetes which reflects a weaker performance

of patients with diabetes (*P*=0.000). In the Intra-extra Dimensional Set Shift (IED) test, the total response time of test was significantly lower in the control group than the diabetic group (*P*=0.006). Also, in Spatial Span (SSP) task, the number of attempts was significantly lower in the diabetic group than healthy subjects which indicated the better performance of the diabetic group in term of this index (*P*=0.028). In the task of Stocking of Cambridge (SOC), the mean moves (in phase 3 moves) was significantly lower in the diabetic group than the control group reflecting a better status in the group with diabetes (*P*=0.006).

As well, In Stop Signal task (SST), the total correct representing the number of correct responses in the steps of movement and stops was significantly higher in the diabetic group than healthy ones (*P*=0.013). No significant difference was found in the remaining tasks.

But, the analysis of results of the tests conducted on patients with diabetes showed that there are direct significant associations between the serum levels of glycosylated hemoglobin (HbA1C) and the Mean correct latency in PRM test (*P*=0.0914), as well as between the Double errors (*P*=0.088) and Within errors in SWM test (*P*=0.05), and the Mean initial thinking time (5 moves) in SOC test (*P*=0.047). These findings reflect better cognitive results in lower levels of HbA1C. However, this association has been also seen in a number of other indices which is not statistically significant. The results of evaluations conducted on the correlation between the indices and duration of diabetes and HbA1C levels are summarized in Table 4.

Table 4. Correlation between cognitive indices and duration of diabetes and HbA1C levels

Test	Measures	Duration of diabetes		Serum level of HbA1C	
		Pearson correlation coefficient	Sig.	Pearson correlation coefficient	Sig.
Motor screening (MOT)	Mean latency	-0.035	0.85	-0.022	0.914
	Mean error	-0.057	0.761	0.276	0.172
Pattern recognition memory (PRM)	Mean correct latency	-0.228	0.226	0.342	0.094
	Span length	0.051	0.787	0.191	0.349
	Total errors	0.004	0.982	0.168	0.412
Spatial working memory (SWM)	Between errors (4 boxes)	-.447	0.013	0.178	0.393
	Between errors (6 boxes)	-0.038	0.843	0.134	0.523
	Between errors (8 boxes)	-0.017	0.93	-0.078	0.709
	Double errors	0.239	0.204	0.349	0.088
	Total errors (4 boxes)	-.449	0.013	0.179	0.392
	Total errors (6 boxes)	-0.032	0.868	0.136	0.517
	Total errors (8 boxes)	0.009	0.964	-0.029	0.891
	Within errors	0.257	0.171	0.387	0.056
Stocking of cambridge (SOC)	Mean initial thinking time (2 moves)	-0.235	0.221	0.223	0.294
	Mean initial thinking time (3 moves)	-0.353	0.061	0.044	0.840
	Mean initial thinking time (4 moves)	-0.098	0.613	0.315	0.134
	Mean initial thinking time (5 moves)	0.089	0.645	0.409	0.047
	Mean moves (2 moves)	0.072	0.706	0.310	0.132
	Mean moves (3 moves)	0.012	0.949	0.094	0.656
	Mean moves (4 moves)	0.016	0.936	0.210	0.324
	Mean moves (5 moves)	-0.002	0.992	-0.181	0.397
Intra-extra dimensional set shift (IED)	Completed stage errors	-0.018	0.924	0.108	0.599
	Completed stage trials	0.035	0.852	0.119	0.562
	Total errors	0.134	0.472	-0.292	0.148
	Total latency	-0.173	0.353	0.216	0.289
Choice reaction time (CRT)	Percent commission trials	-0.048	0.876	0.058	0.865
	Percent correct trials	0.251	0.409	-0.289	0.388
	Mean correct latency	-0.44	0.133	-0.033	0.923

Continuance of Table 1.

Stop Signal Test (SST)	**Direction errors on stop and go trials**	-0.012	0.952	-0.347	0.097
	Total correct on stop and go trials	0.34	0.071	-0.286	0.176
Rapid visual information processing (RVP)	**Probability of false alarm**	0.323	0.205	-0.352	0.218
	Mean latency	0.11	0.747	-0.374	0.361
	Total false alarms	.393	0.035	-0.234	0.271
	Total hits	0.153	0.43	0.088	0.684
	Total misses	0.215	0.263	0.011	0.959

However, no significant correlation was found between the duration of diabetes and various cognitive variables assessed, except the between errors (4 boxes) and Total errors (4 boxes) in the Spatial Working Memory Test (SWM), which revealed a significantly inverse relationship (Table 2).

Discussion

This study aimed to evaluate the cognitive functions in the areas of attention, memory and executive function in children with diabetes compared to their healthy peers. The results showed that except in the case of few variables, no significant difference exists between diabetic children and the control group in terms of different cognitive domains. In some of the indices available for assessment tests, it seems that children with diabetes have a better performance than healthy controls. The cognitive function in children with diabetes, at least in the age of 6 to 12 years, did not show any significant changes with the increasing duration of diabetes. But based on the results of this study, cognitive variables have been shown to be deteriorated with increasing HbA1C values in serum levels.

This study is the evidence suggesting a relationship between diabetes and cognitive functioning in children with diabetes. Previous studies in this area have also marked various results reflecting a disagreement on the relationship between diabetes and cognitive functioning in these ages. in a meta-analysis conducted by Gaudieri *et al*., on the same field of interest, it was concluded that different thresholds of cognition are influenced by diabetes which is intense in children with early onset of diabetes (14). In his study Ohmann also reported that changes in executive functions in adolescents with diabetes are independent of the terms of glycemic control (15). Nevertheless, there remain some studies in this area suggesting no clear and significant correlation between diabetes and cognitive function. Mottus *et al*., in their study to assess the relation between this two conditions drew the conclusion that diabetic patients in their lifelong journey have a poorer cognitive function compared to other individuals, but this poor performance is not due to the impact of diabetes on cognitive function, rather these patients were found to have poorer cognitive function from the beginning of life so that such a difference is established to older ages (16).

In the form of a cohort study to evaluate cognitive function in children with diabetes, Ly TT *et al*., reported that no significant differences in terms of intelligence, memory and emotional functions are found between diabetics and healthy controls (17). With respect to the effect of glycemic control on cognitive function, it seems that the results of this study are consistent with other studies in this field. In other words, glycemic control is perceived to be the most important factor influencing cognitive function in children with diabetes (8). An interesting point raised by the results of this study is that the duration of diabetes was not associated with changes in cognitive functioning in children with diabetes. This could indicate that the duration of diabetes provided by appropriate glycemic control cannot affect the cognitive changes in children.

Some important points should be considered in the analysis of various reports related to different results on the association between diabetes and cognitive functioning in children. The first notion one should take into consideration is that family support and parenting styles in families having a child with diabetes are different from one another. The patterns of parenting are not necessarily similar in different cultures and differences are tailored to match the local requirements (18,19). On the other hand, these supports and family functioning in families of children with chronic health problems are different from those of healthy families (20). Studies have shown that parental support and a responsible parenting style have a positive impact on the cognitive development of children on the one hand, and on a better control of diabetes on the other hand (9,21,22). Accordingly, it can be concluded that even

though diabetes can impose cognitive malfunctioning in children through structural and physical changes, but family support and parenting style can compensate for these changes and prevent the symptoms of cognitive dysfunction. Even in the early onset of diabetes when poor glycemic control has not yet deteriorated the cognitive functioning of children with diabetes, family support may lead to a better and faster cognitive development of children compared to their healthy peers who lack this support. As a matter of course, different styles of child-rearing and family support in different social contexts where these studies are conducted in could explain different findings reported in these studies. One cannot ignore the fact that social support and peer influence can also have similar effects on diabetic children which are also non-identical in different populations (23).

Several social activists in Iran have formed associations for protecting patients with diabetes especially those of younger ages, to provide appropriate support for them in different educational, behavioral, and training areas. However; special attention should be considered by the stakeholders of the health system to expand their role in the management of diabetes (24,25).

The authors also confronted with some limitations in the course of the present study, among which the limited access to children with diabetes to have a larger population is highly noticeable. Also, parents of children with diabetes are reluctant to participate in the research studies due to their daily life problems which is a major drawback in studies conducted on children.

On the other hand, cognitive assessment process and its duration were another major limitation. So that working with computers for cognitive assessment lasting for about an hour was found difficult for children. As well, the lack of evaluation of parenting styles and family and community support has perceived a barrier to study the relationship between these factors and cognitive changes in diabetic children.

The results of this study send out a clear message to families of diabetic children that diabetes has no impact on the cognitive functioning of children provided by maintaining a glycemic control. Also based on the evidence available, it is proposed that the adoption of appropriate parenting styles and family and social support can prevent cognitive changes in children with diabetes. It seems that. It is necessary for schools and social institutions like family to take more prominent roles in their support for diabetic children to prepare the proper cognitive development for children and adolescents with diabetes in partnership with health service providers.

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