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Original Article

# Cognitive function and event related potentials in children with type I diabetes mellitus

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**Abstract.** Type 1 diabetes mellitus is associated with cognitive changes, but the extent of cognition decline depends on age at onset, duration of diabetes and occurrence of attacks of hypoglycemia or ketoacidosis.This study was designed to assess cognitive function in a group of children with type I diabetes mellitus. Forty diabetic children, with mean age at onset of 8.59±2.71 year, were recruited from the Pediatric Department of Assuit University Hospital, Egypt. Forty healthy children matched for age, sex, socioeconomic states were chosen as controls for comparison. Cognition was assessed using the psychometric (Stanford Binet test) and electrophysiologic (Event Related Potentials) tests. Compared to control group, patients reported significant reduction in intelligent quotient, comprehension, abstract visual reasoning, quantitative reasoning, bead memory and total short memory testing for cognitive functions. Prolonged N1, P200, N2 and P300 latencies and reduced P300-N2 amplitude of event related potentials were also reported. Significant negative correlations were identified between in most studied cognitive functions and ketoacidosis or family history of diabetes mellitus. Type I diabetes mellitus and diabetes-related factors are important risks for cognitive deficits in children group of population.

Key words: Type I diabetes mellitus,cognitive functions, event related potentials

## 1. Introduction

Type I diabetes mellitus is associated with cognitive deficits, mild to moderate intellectual and neuropsychological difficulties relative to children without diabetes (1), particularly when diagnosed at earlier age of onset. (2). Children who develop type I diabetes before the age of 7 years are more likely to have poor scores in cognitive tests, independent on the duration of diabetes. This finding is not well explained because of the presence of many confounding variables which may impact this known association and the interaction of the factors remains to be fully elucidated (3). Several factors are found to be associated with lower performance in children with diabetes including male gender (4), lower socioeconomic states, poor metabolic control (5), earlier age at onset, and higher frequency and severity of hypoglycemic episodes (6).

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Event Related Potentials testing is considered an early electrophysiologic determinant of cognitive impairment. Its P300 seems to be the neural correlation of cognitive functions, such as decision making, information processing and short-term memory and could be used as a clinical tool for assessment of cognition (7). P300 may be more sensitive compared to cognitive functions as it detects mild or subclinical impairments while cognitive tests require the presence of prominent impairment in cognitive to be detected (8, 9). This work was aimed to assess cognitive function in a group of children with type I diabetes mellitus and to determine the influence of diabetes-related factors on cognition including age at onset, duration of illness, hypoglycemia, ketoacidosis, family history of diabetes mellitus, and type of insulin therapy.

## 2. Materials and methods

### *2.1. Patients*

Forty consecutive children with type I diabetes mellitus with mean age at presentation was 10.70± 2.74 years (male: 18; female: 22), were selected from a total of sixty four children admitted to the intermediate care unit of the

Table 1. Demographic information of the studied group

| Parameters | Control group (n=40) | Diabetic children (n=40) | p value |
|---|---|---|---|
| Age (mean ±S.D) | 10.70 ± 2.74 | 11.74 ± 2.32 | 0.071 |
| Numbers of educated years (mean ±S.D) | 4.23 ± 2.62 | 5.05 ± 2.14 | 0.127 |
| Social scale scores (mean ±S.D) | 15.84 ± 6.33 | 17.35 ± 6.15 | 0.282 |
| Body mass index (mean ±S.D) | 17.47 ± 4.01 | 16.17 ± 2.07 | 0.073 |

The data are presented as means ± Standard Deviation (S.D.) Statistical significant at p-value < 0.05 compared to normal controls

Pediatric Department of Assuit University Hospital, Egypt over a period of one year . Only children with history of diabetes mellitus were diagnosed according to Zadeh and Wyah (10), of more than 6 months duration were included in our study. Excluded were children with history of head injury, other metabolic conditions, neurological abnormalities, psychological problems or physical disabilities (as deafness or blindness) that may interfere with performance in cognitive testing. This study included forty healthy children matched for age (11.74 ± 2.32) years, sex (male: 20; female: 20), Body Mass Index and socioeconomic states (11) as controls for comparison(table 1). Children with diabetes were divided according to the type of insulin therapy into two subgroups: a) patients on long-acting insulin (n = 29), and b) patients on short-acting insulin (n = 11). This study was approved by Assuit University Hospital ethical committee and all parents or guardians of the participated children gave their written informed consent for participation in our study.

*2.2.Clinical assessment*

Clinical data collected from patients included: 1) age at presentation, 2) age at onset, 3) socioeconomic status, 4) history of hypoglycemia, diagnosed by presence of blood level of less than 60 mg/dl (12), 5) weight, height, body mass index (13), convulsions, diabetic ketoacidosis, diagnosed by presence of disturbed conscious levels, acidosis, dehydration, vomiting, abdominal pain, rapid deep breath and ketonurea and confirmed by acidotic profile in blood gas testing (i.e. pH < 7.3 and $HCO_3$ <16 meq/L) (10), 6) family history of diabetes mellitus, and 7) type of insulin therapy.

*2.3. Laboratory assessment*

For all participants, the following routine laboratory parameters were assessed: 1) fasting blood glucose and after 2 hours levels, 2) complete blood picture, 3) kidney function tests, 4) liver function tests, 5) serum renal functions test (to exclude diabetic nephropathy), liver functions tests, and 6) serum electrolyte levels (sodium, potassium and calcium).

*2.4.Assessment of cognition*

A) All participants (patients and controls) underwent assessment by the Arabic version (14) of Stanford–Binet test (fourth edition) (15) a standardized and well validated psychometric testing used to assess memory, attention, language, and concentration. Stanford–Binet test is formed of Vocabulary, Comprehension, Verbal Relations test, Abstract Visual Reasoning test, Quantitative Reasoning test, Memory for Sentences test, Bead Memory test and Intelligent Quotient. This test is characterized by its acceptability to children, and relevance to daily livings activities in children group of population. The evaluation was performed by a qualified clinical child psychologist, within a time frame ± 2 weeks apart from the Event Related Potentials study and when ketoacidosis and hypoglycemia were corrected.

B) In other settings, recordings of event evoked potentials were done in a dark silent room. Recording electrodes were placed according to international 10-20 electroencephalography system. Event related recording site was Cz (vertex). Reference electrode was applied over A2 (right ear lobule) and the ground electrode was applied on Fpz (midline on the forehead). Potentials were elicited using auditory discrimination task paradigm by presenting series of binaural 1.000 Hertz (standard) versus 2.000 Hertz (target) tones at 70 decibels with a 10 millisecond rise/fall and 40 milliseconds plateau time. Target tones and non-target tones were presented at a rate of 1.1 per second, with target tones occurring randomly with a probability of 0.2 per second. Electrode impedance was maintained at less than 5 ohm. Filter setting was put at 0.5 and 70 Hertz. The participant was asked to close his/her eyes and

Table 2. Comparison between diabetic children and controls in relation to various cognitive functions and event related Potentials

| Cognitive functions | Control group (n=40) | Diabetic children (n=40) | p value |
|---|---|---|---|
| Vocabulary | 44.31 ± 4.87 | 42.40 ± 9.70 | 0.270 |
| Comprehension | 47.21 ± 5.39 | 42.92 ± 7.55 | 0.005 * |
| Verbal Relations test | 91.93 ± 13.66 | 85.60 ± 18.40 | 0.085 |
| Abstract Visual Reasoning test | 93.22 ± 13.57 | 80.20 ± 19.46 | 0.001 * |
| Quantitative Reasoning test | 98.53 ± 12.85 | 88.10 ± 17.86 | 0.004 * |
| Memory for Sentences test | 48.42 ± 7.21 | 45.05 ± 12.33 | 0.139 |
| Bead Memory test | 49.65 ± 6.92 | 42.72 ± 10.10 | 0.001 * |
| Total Short Term Memory | 98.57 ± 17.57 | 85.12 ± 24.70 | 0.006 * |
| Intelligent Quotient | 95.89 ± 11.54 | 83.15 ± 19.60 | 0.001** |
| N1 latency(ms) | 122.97 ± 36.94 | 159.60 ± 43.03 | 0.000*** |
| P200 latency(ms) | 168.32 ± 38.45 | 225.60 ± 44.37 | 0.000*** |
| N2.latency(ms) | 235.05 ± 39.83 | 295.10 ± 47.17 | 0.000*** |
| P300 latency(ms) | 306.65 ± 40.75 | 357.10 ± 51.29 | 0.000*** |
| P300- N2 amplitude (uV) | 14.47 ± 7.28 | 10.36 ± 5.17 | 0.005** |

For statistical comparison student's t-test has been used.
*P value significant <0.05.
Notes: n = number; ms : milliseconds; uv: microvolt.

instructed to mentally count the number of the target but not the frequent (non-target) tones and then asked to report the number of target tones counted at the end of each run. Separate averages for target and non-target tones were obtained. Responses to 30 target and 120 non-target tones were obtained in each trial. All recordings containing some degree of artifact were repeated. Before recording, subjects were familiarized with the two tones and instructed to press a button when target tones were heard. Recordings from Cz were analyzed. Latencies and amplitudes of N100, P200, N200 and P300 waves were measured. Latencies in millisecond were measured from the point where the wave amplitude was at maximum.

P300 latency was measured as the major positive peak after N200, within a range of 250-500 milliseconds. Peaks of waveforms were marked. The first upward deflection following P100 stimulus artifact was marked as N100, and the followings downward-upward and downward deflections were marked as P200, N200 and P300, respectively. Wave amplitudes were measured as peak-to-peak. The amplitudes of N200, and P300 were measured peak to peak from the negative component just before the wave to the maximum positive peak of the wave (16). Event related potentials were done using a Dantec Maglite, TM Copenhagen, Denmark.

### *2.5. Statistical analysis*

Descriptive statistics (mean, Stander Deviation, and percentages) were calculated using the computer software package Statistical Package for the Social Sciences (SPSS) for Windows, Version 16. Results were analyzed using independent-sample T test that did not assume equal variances. A series of correlations coefficient, multiple linear regression analysis and independent sample T test were used to examine the impact of diabetic-related factors on cognitive function and Event Related Potentials. The significance level was set at < 0.05.

## 3. Results

### *3.1. Effect of type I diabetes mellitus on cognition*

History of hypoglycemia, ketoacidosis and family history of diabetes mellitus were recorded in 7 (17.5%), 38 (95%) and 18 (45%) of the studied diabetic children. Compared to control children, patients reported lower score in Comprehension, Abstract Visual Reasoning test, Quantitative Reasoning test, Bead Memory test, Total Short Term Memory and Intelligent Quotient. Event Related Potentials latencies (N1,

Table 3. Correlations between diabetic ketoacidosis and cognitive function

| Cognitive functions | r value | p-value |
|---|---|---|
| Vocabulary | -0.457 | 0.003** |
| Comprehension | -0.448 | 0.004 ** |
| Verbal relations test | -0.472 | 0.002** |
| Abstract visual reasoning test | -0.057 | 0.762 |
| Quantitative reasoning test | -0.376 | 0.017* |
| Memory for sentences test | -0.043 | 0.005** |
| Bead memory test | -0.466 | 0.002** |
| Total short term memory | -0.493 | 0.001** |
| Intelligent quotient | -0.407 | 0.001** |

*, **Correlation was significant at the 0.05 and 0.01 levels (two-tailed), respectively

P200, N2 and P300) were significantly longer and P300-N2 amplitude was significantly reduced (Table 2).

*3.2. Effects of diabetes-related factors on cognition*

For assessment of the effect of diabetic ketoacidosis, history of hypoglycemia, and family history of diabetes on cognitive test performance in children with type I diabetes mellitus, a series of correlation coefficients were calculated. Although, non-non-significant (P>0.05), a negative association was identified between cognitive variables and history of hypoglycemia. Diabetic ketoacidosis had significant negative correlations with different cognitive variables (table 3). Family history of diabetes mellitus was significantly correlated with Comprehension (r=0.332; p=0.035), Verbal Relations test (r=0.316; p=0.047), N1 latency (r=0.334; P=0.035) and P300-N2 amplitude (-0.348; p=0.028). Series of multiple linear regression tests were utilized to assess the effect of duration of illness and age at onset on different cognitive variables. Duration of diabetes followed by age at onset was significant predictors for decline in some measured scales of cognitive function (table 4). Patients on long-acting insulin therapy demonstrated more decline in some cognitive testing including Vocabulary, Comprehension and Verbal Relations test compared to children on short-acting insulin therapy. No differences in Event Related Potential parameter were detected among children on long- and short-acting insulin therapy (table 5).

## 4. Discussion

*4.1. Effect of type I diabetes mellitus on cognition*

This study demonstrated that children with type I diabetes mellitus exhibited clinical and neurophysiological defects in cognition confirming the notion that diabetes itself significantly affects cognitive function (3,17,18, 19).

Event Related Potentials testing is a sensitive neurophysiological tool for early monitoring of cognitive decline. Measurements of the latencies of evoked potentials have been widely used to examine the functional integrity of the central nervous system in diabetic patients (20). Prolonged P300 latency has been found to be associated with cognitive impairment (7,9,21) and increased P300-N200 amplitude is associated with better memory performance. P300 latency is considered as a consequence of attention process, speed of reaction, and immediate memory (22). The hippocampus, thalamus and frontal cortex are considered as possible locations of the P300 generators (23). These structures are important for learning and memory. Previous studies reported abnormalities in central and peripheral components of the brainstem auditory evoked potential in patients with type 1 as well as type 2 diabetes mellitus. The authors concluded that increase in latencies of these evoked potentials provide a central equivalent of reduced conduction velocity in peripheral nerves (20). The putative mechanisms of abnormalities detected in Evoked Potential testing in patients with diabetes mellitus are confounded by many variables. School attendance problems, behavioral difficulties and abnormal myelination are alternative explanations for the observed differences in intellectual ability (18,24). The fact that insulin receptors are expressed in brain areas involved in cognition (particularly the limbic system) provides support for the effect of insulin on neurotransmitters metabolism, synaptic

Table 4. The results of multiple linear regression analysis of Diabetic related factors

| Variables | R | B | Beta | T | P value |
|---|---|---|---|---|---|
| Total Verbal Resonanin | 0.386 | -3.748 | -0.341 | -2.135 | 0390. |
| Duration of illness | | -2.267 | -0.316 | -1.979 | 0550.. |
| Age at onset | | | | | |
| Bead memory | | | | | |
| Duration of illness | 0.396 | -1.834 | 0.907 | -2.02 | 0.050 |
| Age at onset | | -1.313 | 0.592 | -2.22 | 0.033 |
| Total Verbal Short Term Memory | 0.355 | -4.680 | -0.335 | -2.07 | 0.045 |
| Duration of illness | | | | | |
| Intelligent Quotient | | | | | |
| Duration of illness | 0.337 | -3.547 | -0.320 | -1.966 | 0.057 |

The mean difference is significant at the 0.05 level or less.

Table 5 Cognitive function and Event Related Potentials in diabetic children in relation to the type of insulin

| Cognitive functions | Diabetics with long-acting insulin (n=29) | Diabetics with short-acting insulin (n=11) | P value |
|---|---|---|---|
| Vocabulary | 40.17 ± 7.92* | 48.27 ± 11.807 | 0.016 |
| Comprehension | 41.48 ± 6.79* | 46.72 ± 8.46 | 0.049 |
| Verbal relations test | 81.86 ± 5.87164* | 95.45 ± 21.63 | 0.035 |
| Abstract visual reasoning test | 79.51 ± 16.21 | 82.00 ± 27.14 | 0.724 |
| Quantitative reasoning test | 87.17 ± 15.12 | 90.54 ± 24.39 | 0.60 |
| Memory for sentences test | 43.79 ± 12.21 | 48.36 ± 12.63 | 0.302 |
| Bead memory test | 41.24 ± 10.10 | 46.63 ± 9.43 | 0.133 |
| Total short term memory | 81.89 ± 24.42 | 93.63 ± 24.50 | 0.183 |
| Intelligent Quotient | 80.27 ± 18.18 | 90.72 ± 22.03 | 0.134 |
| N1 latency (ms) | 154.62 ± 40.27 | 172.72 ± 49.18 | 0.240 |
| P200 latency (ms) | 221.51 ± 41.61 | 236.36 ± 51.53 | 0.351 |
| N2 latency (ms) | 294.93 ± 51.54 | 295.54 ± 35.18 | 0.971 |
| P300 latency (ms) | 356.17 ± 56.06 | 359.54 ± 38.127 | 0.855 |
| P300- N2 amplitude (uV) | 10.70 ± 5.11 | 9.45 ± 5.46. | 0.501 |

For statistical comparison student's t-test has been used.
*P value significant <0.05.

plasticity and cognition and thus relative insulin deficiency during childhood neurodevelopment has to be considered (17). Brain damage in mesial temporal or prefrontal regions (25) may affect memory process to such extent that person loss the ability to efficiently encode new information or retain recently acquired knowledge about their social and physical environment. For this reason when memory are compromised, the child performs more poorly in a wide range of cognitive measures including verbal intelligence, academic achievement and may never attain full vocational potentials.

Several mechanisms for cognitive impairment in diabetes are suggested including: impaired autoregulation and decreased cerebral blood flow, altered brain-energy metabolism, altered Neuro-transmitter metabolism, structural defects of brain (i.e., decreased brain volume and weight and loss of cortical neurons), non-enzymatic glycosylation of brain tissue and increased CNS sorbitol levels (24). More recently, Araki and Ito (26) reported that the accumulation of advanced glycation

endproducts (AGEs) (N-epsilon-carboxymethyllysine) as measured by enzyme immunoassay may exert several actions on central nervous system and may be implicated in the pathogenesis of diabetic complications and aging.

*4.2. Impact of diabetic-related factors on cognitive function*

This study reported that diabetic–related factors as prolonged duration of illness, earlier age of onset, and family history of diabetes are directly related to cognitive decline in children with diabetes. Several previous studies found that early age at onset, duration of diabetes, and positive family history were significantly associated with impairment of complex psychomotor skill and children tended to have developmental delay, learning difficulties at school and higher rates of attention and hyperactivity disorders, although prediction of individual outcome is difficult to determine (26-28). Some long-term follow up studies found that diabetic adults with poor performance in intellectual testing had earlier onset of type I diabetes mellitus that was also associated with mild central brain atrophy. However, the difference observed in brain structure support an organic contribution to their etiology but don't exclude a coexistent contribution to psychosocial factors (19).

In this study, although, negative association was identified between cognitive testing scores and the occurrence of hypoglycemia, however, this association did not reach a significant level. Studwicksk et al (29) and Wisocki,(30) did not report an association between seizures or coma that even occurred at early childhood and cognitive decline. In contrast, Ferguson and his colleagues (17) reported that the cognitive impairment associated that occurred at early onset diabetes depended on early exposure to hypoglycemia attacks. The authors concluded that hypoglycemia should be avoided in all children with diabetes. We found significant association between diabetic ketoacidosis and cognitive decline (20).

In this study, significantly lower scores were obtained in Vocabulary and Comprehension testing in children treated with long-acting insulin compared to those on short-acting insulin. Matyka et al. (31) suggested that young children on conventional insulin regimens are at high risk for profound asymptomatic nocturnal hypoglycemia which is difficult to predict. Although, the authors did not observe short-term effect on cognitive functions, however, long-term effect was suspected. This information should be used in assessing the benefits and risk of light glycemic control of type I diabetes at very young age. Treatment decisions are complex and must also take into account the clear benefits of light control in reducing complications.

## 5. Conclusions

In Conclunun type I diabetes mellitus is an important risk for cognitive deficits in children group of population. Earlier age at onset, prolonged duration of illness and long-acting insulin may increase the risk for negative cognitive function in children with diabetes.

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