Cognitive Function in Younger Type II Diabetes

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OBJECTIVE — To examine central nervous system involvement as a possible complication of diabetes by performing a comprehensive neuropsychological evaluation of relatively young (age <55 years) NIDDM patients and a group of control subjects.

RESEARCH DESIGN AND METHODS — A cross-sectional comparative study of 28 patients, with duration of diabetes 5–18 years (mean ± SD 8.3 ± 3.2 years), screened for acceptable glycemic control and absence of hypoglycemia on the day of examination, compared with 28 demographically similar, nondiabetic control subjects. Neuropsychometric tests performed were Mini-Mental Status Examination (MMSE), Neurobehavioral Cognitive Status Examination (NCSE), and P300 latencies (endogenous evoked potentials).

RESULTS — Seven (25.0%) patients reported history suggestive of cognitive impairment during day-to-day activities, and 17 (60.7%) had distal symmetrical polyneuropathy. Average P300 latencies were significantly delayed among the diabetic patients compared with the control subjects (349.5 ± 28.2 vs. 312.9 ± 19.3 ms; $t = 5.68$, $P < 0.001$). Although there was no significant difference in MMSE scores, compared with control subjects significantly more patients had impairment in NCSE tests of attention ($\chi^2 = 7.38$, $P < 0.01$), repetition ($\chi^2 = 4.073$, $P < 0.05$), and memory ($\chi^2 = 5.83$, $P < 0.05$), while there was no significant difference in tests of comprehension, naming, construction, and calculation. Duration of diabetes, HbA_{1c} levels, and the presence of distal symmetrical polyneuropathy among patients each did not correlate with any of the parameters of cognitive function evaluated. Higher blood glucose levels during the electrophysiological testing were associated with less delay in P300 latencies among the patients.

CONCLUSIONS — Central nervous system impairment, manifesting as mild impairments in certain cognitive skills, should be recognized as a possible complication of long-standing NIDDM, even in relatively younger individuals.

Central nervous system involvement is increasingly recognized as a possible complication of diabetes (1). Most previous studies were done on patients with type I diabetes, who have been noted to perform worse than expected on a wide range of tasks, including measures of learning, problem solving, and mental and motor speed; however, the magnitude of these effects has tended to be inconsistent from study to study (2). Relatively fewer studies, differing widely in setting and methodology, have investigated cognitive functions in type II diabetic patients. Some of these studies found no difference between patients and control subjects, and others found significant differences in certain cognitive skills (3–8). Most of these studies included only elderly type II diabetic patients, in whom advanced age or various other comorbid conditions could be influencing performance in cognitive tests.

Whether the diabetic milieu by itself can influence cognitive functions during the course of the disease is an open question with important scientific and social implications. We tried to remove the confounding influences of aging, recurrent hypoglycemic attacks, or other chronic diseases (e.g., cerebrovascular attacks) by selecting relatively young and healthy patients with type II diabetes with no prior history of hypoglycemia, and we compared their cognitive functions with a demographically similar nondiabetic control group. The combination of psychometric and electrophysiological techniques permitted a comprehensive evaluation of neuropsychological aspects in the subjects.

RESEARCH DESIGN AND METHODS

— A total of 28 individuals with type II diabetes, who were receiving care from the medical outpatient department for the control of diabetes, and the same number of nondiabetic control subjects were selected, after taking their informed consent to take part in the study. All control subjects were spouses, siblings, or similar-ranking colleagues of the enrolled diabetic subjects. The similarity of the two groups with regard to their mean educational level, age, and presence of hypertension supports the notion that except for the diagnosis of diabetes, the groups were similar with regard to major confounding variables for cognitive function (see Table 1).

The duration of diabetes ranged from 5 to 18 years, with a mean ± SD of 8.3 ± 3.2 years. Five (17.8%) of the diabetic subjects were on diet and exercise control only, and twenty-three (82.1%) were on oral hypoglycemic agents for a duration of 5.87 ± 2.60 years (range: 2–12 years). None of the subjects included in the study ever required insulin for control of hyperglycemia. Patients reporting previous episodes of symptomatic or incidentally documented hypoglycemia or ketoacidosis were excluded from the study. Other exclusion criteria were the following: intake of any "centrally active" medications (e.g., sedatives, anticonvulsants); history of any medical, neurological, or psychiatric disease expected to interfere with cognitive faculties (e.g., hypothyroidism, visual impairment, stroke, depression); and the

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DCCT, Diabetes Control and Complications Trial; DSP, distal symmetrical polyneuropathy; MMSE, Mini-Mental Status Examination; NCSE, Neurobehavioral Cognitive Status Examination.

Table 1—*Clinical characteristics of diabetic subjects and control subjects studied*

Characteristics	Control subjects	Diabetic subjects	*P* values
n	28	28	
Age (years)	47.5 ± 5.8	46.7 ± 5.6	NS
Sex (M/F)	14/14	18/10	
BMI (kg/m^2)	22.7 ± 2.7	24.4 ± 3.4	NS
Years of formal education	11.6 ± 3.5	12.0 ± 4.6	NS
Profession			
Clerical/accounting	11 (39.2)	9 (32.1)	
Business	3 (10.7)	4 (14.3)	
Professional	3 (10.7)	5 (17.9)	
Others	11 (39.2)	10 (35.7)	
Prevalence of major medical problems			
Hypertension	11 (39.3)	11 (39.3)	NS
Ischemic heart disease	3 (10.7)	3 (10.7)	NS
Retinopathy		6 (21.4)	<0.001
Blood glucose			
Fasting (mg/dl)	72.2 ± 6.8	109.8 ± 17.7	<0.001
2-h postprandial (mg/dl)	96.2 ± 1.8	142.6 ± 18.6	<0.001
HbA_{1c} (%)		8.01 ± 0.94	

Data are means ± SD or *n* (%). $P > 0.05$ was considered nonsignificant.

use of alcohol, opioids, or any other psychotropic substances on a regular basis.

All control subjects were confirmed to be nondiabetic by using the World Health Organization (1985) criteria (9) for fasting and 2-h postprandial glucose. All patients were within "acceptable" range (<200 mg/dl) of postprandial glucose levels, and none were hypoglycemic, on the day of the examination.

Psychometric testing

The Mini-Mental Status Examination (MMSE) is a brief screening test for cognitive dysfunction with demonstrated reliability and validity (10) based on a univariate or "global" model of "organicity." The Neurobehavioral Cognitive Status Examination (NCSE) independently assesses multiple domains of cognitive functioning and thereby provides the clinician with a differentiated profile of the patient's cognitive status. It uses a screen and metric approach that allows cognitively intact people to complete the examination quickly, devoting more time to areas of impaired functioning, if present. The scores obtained in each subtest are interpreted as in normal or impaired range. Comparative studies have revealed high sensitivity (>99%) but low specificity rates for NCSE as compared with MMSE (11).

The psychometric tests (MMSE and NCSE) were administered to all the subjects adhering strictly to the procedure outlined by the developers. For patients from non–English-speaking background, standardized Hindi versions of both the tests were administered. Both the tests were administered at the same session, but the sequence of the tests was changed in a random manner.

Electrophysiological evaluation

Endogenous-event–related potentials were obtained, using the tonal P300 oddball paradigm, on all the participating subjects. The P300 wave is a late cortical neurophysiological event and is considered to reflect the speed of neuronal events underlying information processing. It appears to be strongly associated with attention and short-term memory (12). The target tone (2 kHz) and the nontarget tone (1 kHz) used were presented over headphones at an intensity of 70 dB. They were presented with a probability of 20% to the left and right ears separately. The subject was asked to silently count all the rare target tones, ignoring the nontarget tones, and to report the total at the end of the test (target test). Evoked potentials were recorded from scalp locations referred to linked mastoids, using zinc-lead electrodes. The target and nontarget responses were averaged separately. Latency measurements were made by a rater from the peak point in the designated interval.

Statistical methods

The χ^2 test and two-sample Student's *t* test (*t*) were applied. A *P* value >0.05 was taken as indicative of nonsignificant difference between the two groups compared. Pearson's correlation coefficients (*r*) were calculated, and any value, positive or negative, more than the critical value (two-tailed, 0.05) of 0.373 was taken as indicative of significant correlation.

RESULTS

Neurological complications

In an attempt to standardize the clinical evaluation of neurological impairment, the clinical examination protocol used by the Diabetes Control and Complications Trial (DCCT) for determining distal symmetrical polyneuropathy (DSP) was used (13). A two-point scale (present, not present) was used. Among all the subjects, seventeen (60.7%) of the patients and none of the control subjects were found to be having DSP. The patients with DSP did not have a

Table 2— *Number of subjects with impaired scores in NCSE subtests*

Test	Control subjects (*n* = 28)	Patients (*n* = 28)	χ^2 test	*P* value
Orientation	0	0	—	NS
Attention	6 (21.4)	17 (60.7)	7.38	<0.01
Comprehension	0	3 (10.7)	—	NS
Repetition	2 (7.1)	9 (32.1)	4.07	<0.05
Naming	0	0	—	NS
Construction	5 (17.9)	12 (42.9)	3.04	NS
Memory	4 (14.2)	12 (42.9)	5.83	<0.05
Calculation	3 (10.7)	5 (17.9)	0.15	NS
Similarities	2 (7.1)	5 (17.9)	0.65	NS
Judgment	0	1 (3.6)	—	NS

Data are *n* (%).

Table 3—*P300 latencies among control subjects and patients*

Parameter	Mean	SD	Minimum	Maximum
Control subjects				
P300 left	310.6	18.4	284.8	368.0
P300 right	315.0	26.1	268.0	406.4
P300 average	312.9	19.3	289.6	387.2
Patients				
P300 left	350.0	33.9	291.0	409.6
P300 right	349.0	30.8	297.6	403.6
P300 average	349.5	28.2	300.7	406.6

P300 latencies measured in milliseconds, $n = 28$ for both groups.

significant difference in their average P300 latencies when compared with patients without DSP ($t = -0.217$, $P > 0.05$).

Psychometric tests

Subjects were screened for depression, distractibility, and exhaustion on the day of the examination. No significant difference was found in the total MMSE scores among the control subjects and patients (29.3 ± 0.9 and 27.4 ± 1.8, respectively, $P > 0.05$). Age, duration of diabetes, HbA_{1c}, prevailing blood glucose values, and the P300 latencies had no significant correlation with the MMSE scores.

In the NCSE, the number of patients with scores in the impaired range was significantly more than that of the control subjects in the subtests of attention, repetition, and memory. In the other subtests of comprehension, calculation, construction, similarity, and judgment, although more patients had impaired scores than the control subjects, the difference was not significant (Table 2). Nineteen (67.9%) of the patients and seven (25.0%) of the control subjects had at least one of the subtest scores below normal range. There was no significant correlation of patient's below-normal scoring in the various NCSE subtest with age, duration of disease, parameters of glycemic control, and P300 latencies.

Electrophysiology

The difference between the patient and control groups was statistically significant with respect to left-sided ($t = 5.41$, $P < 0.001$), right-sided ($t = 4.46$, $P < 0.001$), and an average of left-sided and right-sided P300 latencies ($t = 5.68$, $P < 0.001$) (Table 3). The average P300 latencies did not correlate with age, duration of diabetes, or HbA_{1c}, but there was a significant negative correlation with the prevailing blood glucose levels at the time of examination, among the diabetic patients (Fig. 1).

CONCLUSIONS — To date, most studies done on patients with type II diabetes indicating impaired cerebral functions have included older subjects (3–8). Because the patterns of cognitive impairment associated with normal senescence are similar to the patterns reported in elderly diabetic subjects (14), the pathogenetic mechanisms present with advancing age and with diabetes may have been acting synergistically, resulting in some of the observed neurobehavioral impairments. Taking cognizance of this fact, patients <55 years of age were included in our study so as to minimize the impact of aging on their cerebral function. Within the study group, age did not have a significant impact on either the performance in psychometric tests or the P300 latencies. Similar observations indicating no correlation of age with psychometric test scores have been previously reported (7), while others have observed a tendency toward lower scores among older type II diabetic patients (8).

In the present study, there was no significant correlation of duration of disease with cognitive function abnormalities in contrast to the observation that the duration of disease is a major predictor of most other diabetic complications, such as nephropathy and retinopathy (15). Cognitive functioning in type II diabetic patients correlated with duration of disease in some (8) but not in other studies (3,7).

We did not find a statistically significant correlation among the HbA_{1c} values of the patients and their performance on the psychometric tests of cognitive functioning and their P300 latencies. However, there was a trend for average P300 latencies being less delayed in patients with higher blood glucose on the day of examination ($r = -0.436$). There was no significant correlation between the blood glucose levels and the performance in psychometric tests used by us. Worall et al. (8) also reported that although, as a whole, patients with type II diabetes had lower cognitive function test scores, the scores tended to be higher among those patients with higher-than-average HbA_{1c} levels. It can be postulated that over a long duration, diabetes produces impairment in cognitive function, which may be related to a state of relative neuroglycopenia induced by decreased glucose transfer across the blood-brain barrier, as previously demonstrated in animal studies (16). In such a situation, higher blood glu-

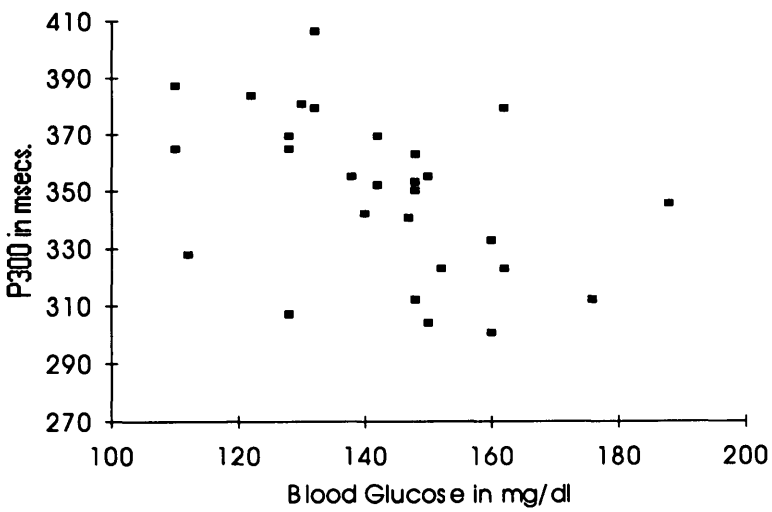

Figure 1—*P300 latencies (average of right and left sides) of patients compared with prevailing blood glucose levels ($r = -0.436$, Pearson's correlation coefficient).*

cose levels on a short-term basis might lead to improvement in measures of cognitive function.

In the overall analysis of results obtained in the psychometric tests, the diabetic patients had impaired performance in tests of attention, repetition, and recent memory, as compared with control subjects. This pattern of impairment may be compatible with a defect in the retrieval of recently learned material and of information storage mechanisms, as has been observed in previous studies on older type II diabetic patients (3,7,8). A total of seven (25.0%) patients also reported, upon direct questioning, a history suggestive of a cognitive impairment, such as forgetfulness, as evidenced by misplacing things and forgetting important events, addresses, or telephone numbers, and of cognitive symptoms that may have a direct bearing on day-to-day functioning of a person in the home or office setting.

Mooradian et al. (3), in a study done on elderly (>60 years) type II diabetic patients, did not find any significant differences in visual checkerboard and auditory tonal stimuli–elicited P300 latencies among patients and nondiabetic age-matched control subjects (3). However, a trend toward longer latencies was seen in certain locations (subcomponents A and B at F_z and C_z electrode positions) among the diabetic patients. In the present study, the observations of a statistically significant difference between the patient and control group with regard to their P300 latencies are of particular value because the presumed influence of age on endogenous-evoked potentials has been minimized by selecting a relatively younger subset with type II diabetic patients and matching them carefully with the age of control subjects.

In prior studies done on type II diabetic patients, some investigators observed a definite correlation between presence of peripheral neuropathy and performance in the tests of cognitive functions (7), while others did not find any correlation (3). These discordant findings may be a consequence of several factors, including different sample size and selection, different criteria for detection of peripheral neuropathy, and different batteries of tests used for the detection of psychomotor impairment. Despite using standard protocols for detecting neuropathy and valid tests, such as the NCSE and the P300 latencies, we were unable to demonstrate any association between peripheral neuropathy and cognitive impairment. It might be surmised that the factors responsible for genesis of peripheral neuropathy in diabetes may be different from those responsible for the involvement of the central nervous system.

In conclusion, on the basis of observations of the present study, we suggest that cognitive dysfunction should be recognized as a definite complication of long-standing type II diabetes, even in relatively younger individuals. Improper and irregular compliance with therapy or even accidental overdoses may be a direct consequence of such subtle or overt cerebral malfunctioning. We recommend that awareness should be created among health professionals involved directly or indirectly in the care of diabetic patients and the lay public about the association of impairment of cognition and diabetes. Education and treatment strategies for diabetic individuals may have to be altered accordingly.

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