Characteristics of neuropsychological functions in inpatients with poorly-controlled type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: It has been suggested that type 2 diabetes is associated with cognitive impairment. We investigated the neuropsychological profile of inpatients with poorly controlled type 2 diabetes and assessed the effects of clinical factors on neuropsychological functions.

Materials and Methods: Forty-two patients with type 2 diabetes and 32 non diabetic control subjects were matched for age, sex ratio, and level of education. Attention & working memory, processing speed, verbal memory, visuospatial memory, visuoconstruction, and executive function were tested. Information about physical function, alcohol use, hypertension, dyslipidemia, and myocardial infarction was retrieved from personal interviews and medical records.

Results: Diabetic patients demonstrated mild cognitive deterioration in attention & working memory, processing speed, verbal memory, and executive function. In particular, neuropsychological decline became prominent when tasks related with speed and verbal stimuli became unstructured and complex. Age was significantly associated with the majority of neuropsychological tests, whereas tasks dealing with working memory and executive function were associated with age only in the diabetic group. Duration of diabetes was associated with Backward Digit Span.

Conclusions: Accelerated aging had a major influence on cognitive decline in the diabetic group, whereas diminished performance in working memory and executive function might have been more related to diabetes-related cognitive impairment. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00170.x, 2012)

INTRODUCTION

Epidemiological studies suggest that the prevalence of diabetes mellitus has been increasing at a rapid rate in developed countries. In the Western Pacific region, which includes Japan and 38 other countries, 76.7 million people are reported to have diabetes, and more than one million adults will die of diabetes-related causes in 2010[1]. According to the National Survey of the Actual Situation of Diabetes Mellitus, the estimated number of patients in Japan suspected of having diabetes mellitus was about 8.9 million, which represented a sharp increase compared to the results of the same survey conducted in 2002 (7.4 million) and 1997 (6.9 million)[2]. In Japan, approximately 95% of diabetic cases are classified as type 2 diabetes[3]. Environmental factors such as eating habits and exercise are believed to play a significant role in the pathogenesis of the disease.

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In addition to affecting the microvessels of the eyes, kidneys, and peripheral nerves, diabetes has been observed to affect the central nervous system, resulting in cognitive decline among patients with type 2 diabetes[4]. Furthermore, diabetes is associated with an increased risk of dementia, including Alzheimer's disease and vascular dementia[5]. Case-control studies indicated cognitive impairment with brief cognitive screening and verbal memory and processing speed tests, although the findings were less consistent for nonverbal memory and executive function tests[6,7]. However, not all studies have suggested these cognitive impairments. Differences in methods and study designs such as demographic and diabetic characteristics have made some results inconclusive. Inconsistencies may also be due to differences in the control of confounding factors. Although vascular risk factors, such as cardiovascular and cerebrovascular diseases, hypertension, dyslipidemia, and cigarette smoking, as well as psychological distress and lifestyle factors including alcohol consumption, have been suggested to influence cognitive functions[8], the relation between these factors and neuropsychological functioning has not been examined in detail. Age is also an important demographic factor for cognitive impairment in type 2

diabetes. The characteristics of diminished neuropsychological functioning in diabetes resemble the pattern of cognitive decline described in normal aging[9]. Several studies indicated accelerated brain aging caused by diabetes mellitus[10,11], and thus assessing broad neuropsychological aspects and providing descriptive evaluations after controlling confounding factors such as age are necessary.

Few studies have evaluated the neuropsychological functions of diabetes in patients with relatively poor glycemic control. We performed neuropsychological tests on hospitalized patients with poorly controlled diabetes and examined the neuropsychological characteristics of patients with poor glycemic control.

Using a case-control design, the present study aimed to examine the broad neuropsychological aspects and the relationship between confounding factors and declining neuropsychological functions in hospitalized patients with poorly controlled type 2 diabetes.

METHODS

Participants

Between November 2005 and October 2007, 42 inpatients with type 2 diabetes and 32 non-diabetic patients as controls were included. The patients were hospitalized for 2 weeks for diabetic education. Healthy control subjects did not meet criteria for diabetes (HbA1c < 5.8% and fasting plasma glucose < 110 mg/dL). The two groups were matched for age, sex ratio, and education. Inclusion criteria were: (i) diagnosis of type 2 diabetes by a diabetes consultant; (ii) fluency in Japanese; (iii) absence of a documented history of mental retardation or other major psychiatric disorders, head trauma, or macrovascular events; and (iv) absence of a history of alcohol or drug abuse. Prevalent diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dL and HbA1c $\geq 6.5\%$. Depression with >15 points on the Japanese version of the Beck Depression Inventory Second Edition (BDI-II)[12] was excluded on consultation with a psychiatrist for depression. Similarly, dementia with <24 points on the Mini Mental State Examination[13] and <1 on the Clinical Dementia Rating[14] were excluded by fulfilling the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The value for HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society: JDS (%) + 0.4%, considering the relational expression of HbA1c (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP).

The Tokyo Medical and Dental University Hospital research review board approved the study and granted formal access to the patients. All participants were informed of the nature, risks, and benefits of participation, and written consent was obtained during the recruitment phase. Seventy-four patients were approached of which 32 were excluded and 42 were eligible. Patients were excluded because of incomplete data due to the duration of hospitalization (26 patients), poor vision related to cataract (four patients), and refusing to participate in the study (two patients).

Clinical information on diabetes and confounding factors

The participants were asked about their educational level (years), the duration of diabetes (years), history of heart disease, the type of treatment for diabetes, alcohol consumption, and smoking status. Alcohol consumption was classified into three categories: none, a few drinks per month and few drinks per week, and daily. Smoking status was classified into two categories: never/formerly and currently. The following confounding variables, which were assessed during hospitalization, were obtained from medical records. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medication. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥ 140 mg/dL or use of cholesterol-lowering agents. Body mass index (BMI) was calculated as weight (kg)/height (m^2); the participants were categorized as normal or overweight based on established criteria (overweight, BMI > 25; normal, BMI 18.5–24.9).

Neuropsychological assessment

Neuropsychological tests were performed on all participants by a trained neuropsychologist unaware of the diagnoses of the participants. All neuropsychological measures were selected to cover the major cognitive domains, applying the classification of Lezak[15]; the duration of the test session was approximately 80 min.

'Attention and working memory' was assessed by the Forward and Backward Digit Span of a Japanese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[16]. The Digit Span Backward is an activity that calls upon the working memory, as distinct from the efficiency of attention measured by the Digit Span Forward[15]. 'Processing Speed' was assessed by the Trail Making Test (TMT)[17] and the Digit Symbol of the WAIS-R. The TMT consists of two parts, TMTA and TMTB, and measures visual scanning involving motor speed and attention function. The Digit Symbol is a test of psychomotor performance. 'Verbal Memory' was measured by two tests: (i) word list recall (immediate and delayed) and word list recognition from the Japanese version of the Rey Auditory Verbal Learning Test (RAVLT)[18]; and (ii) immediate and delayed recall of stories from Logical Memory (LM) of the Wechsler Memory Scale-Revised (WMS-R)[19]. The RAVLT measures immediate memory span, learning ability and the efficiency of retrieval. The LM, a test of memory for a story, measures abilities of immediate and delayed recall when more information are presented than can be fully grasped. 'Visuospatial memory', involving visual recall, was assessed by a delayed recall trial of the Rey-Osterrieth Complex Figure Test (ROCFT)[20]. 'Visuoconstruction', measuring visuospatial and visuomotor integration, was assessed by a copy trial of the ROCFT. 'Executive Function' was measured by the Wisconsin Card Sorting Test (Keio-version; KWCST)[21] and the Verbal Fluency Test (VFT), which includes two category-naming tasks and three letter-fluency tasks. The KWCST involves problem-solving and flexible planning. The VFT

measures verbal productivity within a time limit and a subject's strategy of word searching. The scores used for the analyses were the number of correctly recalled sequences for the Digit Span; the number of seconds to complete the TMT; the number of words and figures generated on VFT and the Digit Symbol; the number of correct words for the LM; the total number of words remembered in five learning trials and the number of words remembered in delayed and recognition trials for the RAVLT; and the number of categories achieved and the number of perseveration for the KWCST. For the ROCFT, we calculated the score according to the original scoring method[20].

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 18.0 (SPSS Inc., Cary, NC, USA). For descriptive data, the patient group and the control group were compared for the demographic and health-related variables, using Student's t-tests for parametric data and chi-square tests for categorical data. Differences between the patient and control groups for the neuropsychological outcomes were assessed with Student's t-tests.

The relationships between impaired neuropsychological measures of the diabetic group and diabetes-related variables including age, sex, years of education, HbA1c, fasting blood glucose, insulin treatment, and duration of diabetes were analyzed using multiple linear regression. Age was included as an independent variable because it was assumed to be a significant factor in cognitive outcomes in previous studies. In the control group, age, sex, years of education, HbA1c, and fasting blood glucose were analyzed using multiple linear regression.

Moreover, to examine if patients with and without hypertension, dyslipidemia, and heart disease differed in neuropsychological functioning, the patients were divided into two groups based on comorbidity of hypertension, dyslipidemia, and heart disease. Between-group differences were assessed using Student's t-tests. Additionally, the influence of insulin treatment, obesity, alcohol consumption, and smoking status on neuropsychological outcomes was examined using Student's t-tests or analysis of variance (ANOVA). In the control group, dyslipidemia, obesity, alcohol consumption, and smoking status were analyzed.

RESULTS

The demographic and medical variables used in the study are summarized in Table 1. No significant differences were observed between the diabetic and control groups with regard to age, sex distribution, and level of education. The diabetic patients had had diabetes for 11.5 ± 9.7 years on an average. The average HbA1c level was 9.5%, which indicated poorly controlled diabetes. Overall, 69.0% patients had hypertension, as in the case with patients with dyslipidemia. Individuals with diabetes were more likely to have elevated BMI ($P = 0.009$), HbA1c ($P < 0.001$), fasting blood glucose ($P < 0.001$), and BDI-II ($P = 0.024$) levels. Of the patients with diabetes, 29 (69%) were receiving insulin therapy.

Table 1 | Demographic and medical history characteristics of the type 2 diabetes and control samples

	Type 2 diabetic group	Non-diabetic control group	P-value
N	42	32	–
Male/female ratio	26/16	18/14	0.481
Age (SD)	62.4 (8.5)	63.8 (4.7)	0.921
Years of education (SD)	13.7 (1.8)	14.5 (1.9)	0.090
MMSE	27.9 (1.8)	28.7 (1.7)	0.073
HbA1c: % (SD)	9.5 (1.8)	5.5 (0.3)	<0.001***
Fasting blood glucose: mg/dL (SD)	150.2 (38.9)	93.9 (8.2)	<0.001***
Diabetes duration (SD)	11.5 (9.7)	–	–
BMI (SD)	24.0 (3.8)	22.1 (2.2)	0.035*
Hypertension: n (%)	29 (69.0)	0	<0.001***
Dyslipidemia: n (%)	29 (69.0)	3 (9.4)	<0.001***
Diabetic treatment: n			
Diet	6		
OHA	7		
Insulin	29		
Heart disease: n	6	0	0.028*
Alcohol consumption: n			
None	20	4	
A few per month	6	12	
A few per week	4	3	
Daily	12	13	
Smoking status: n			
Never	25	31	
Former	7	1	
Current	10	0	
Scores of BDI-II	6.5	3.4	0.024*

*$P < 0.05$; ***$P < 0.001$.
MMSE, Mini Mental State Examination; BMI, body mass index; OHA, oral hypoglycemic agents; BDI, Beck Depression Inventory.

With regard to the neuropsychological functions, the patient group performed significantly worse than the control group on Backward Digit Span, ($P = 0.016$), TMTB ($P = 0.005$), total RAVLT ($P = 0.017$), immediate LM ($P = 0.023$), delayed LM ($P = 0.005$), TMTA ($P = 0.001$), Digit Symbol ($P < 0.001$), KWCST category ($P = 0.045$), KWCST perseveration ($P = 0.008$), VFT category ($P = 0.001$), and VFT letter ($P = 0.013$). Specifically, a significant difference was observed only in trial 1 of RAVLT ($P = 0.001$). No significant differences were observed in Forward Digit Span, delayed RAVLT, RAVLT recognition, and ROCFT between the diabetic and control groups (see Table 2).

In multiple linear regression analysis of the diabetic group, age was significantly associated with TMTB ($\beta = 0.576$, $P < 0.001$), TMTA ($\beta = 0.534$, $P < 0.001$), Digit Symbol ($\beta = -0.698$, $P < 0.001$), KWCST category ($\beta = -0.645$, $P < 0.001$), KWCST perseveration ($\beta = 0.483$, $P = 0.001$), VFT category ($\beta = -0.379$, $P = 0.013$), and VFT letter ($\beta = -0.481$, $P = 0.001$). Duration of the disease was associated with Backward Digit Span ($\beta = -0.455$, $P = 0.002$). LM showed no

Table 2 | Raw-scores of neuropsychological functions in the type 2 diabetes and control samples

	Type 2 diabetic group Mean (SD)	Non-diabetic control group Mean (SD)	P-value
Attention and working memory			
Digit span forward	6.5 (2.2)	7.2 (1.9)	0.149
Digit span backward	5.6 (1.7)	6.5 (1.4)	0.016*
Processing speed			
TMT part A	125.8 (49.2)	100.1 (29.3)	0.011*
TMT part B	161.4 (71.0)	124.5 (36.1)	0.005**
Digit symbol	49.3 (11.4)	59.6 (10.1)	<0.001***
Verbal memory			
RAVLT total trials 1–5	41.4 (8.5)	46.6 (9.9)	0.017*
RAVLT trial 1	4.5 (1.2)	5.8 (1.8)	0.001**
RAVLT trail 2	7.3 (1.9)	8.2 (2.5)	0.068
RAVLT trail 3	8.8 (2.3)	10.0 (2.7)	0.057
RAVLT trail 4	10.1 (2.4)	11.0 (2.4)	0.089
RAVLT trail 5	10.7 (2.2)	11.7 (2.0)	0.059
RAVLT delayed trial	8.6 (2.9)	9.7 (3.2)	0.121
RAVLT recognition trial	14.0 (1.7)	13.8 (1.6)	0.785
Logical memory A	17.8 (6.7)	21.5 (6.8)	0.023*
Logical memory B	12.6 (5.6)	16.5 (6.1)	0.005**
Visuospatial memory			
ROCFT delayed recall trial	15.9 (6.1)	17.6 (6.3)	0.236
Visuoconstruction			
ROCFT copy trial	33.7 (2.4)	34.6 (1.9)	0.098
Executive function			
KWCST category	3.2 (2.0)	4.2 (1.8)	0.045*
KWCST perseveration	6.9 (6.9)	3.2 (3.7)	0.008**
Verbal fluency category	25.7 (6.5)	31.3 (7.3)	0.001***
Verbal fluency letter	24.1 (9.2)	29.7 (9.5)	0.013*

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test; ROCFT, Rey-Osterrieth Complex Figure Test; WCST, Wisconsin Card Sorting Test.

relationship with diabetes-related factors and age. In controls, Digit Symbol ($\beta = -0.450$, $P = 0.027$) were related with age. Moreover, HbA1c was found to be associated with Backward Digit Span ($\beta = -0.520$, $P = 0.009$).

In subsequent analysis, the relationships between vascular risk factors and neuropsychological results in the diabetic patients were examined. Neuropsychological results did not differ whether the patient had hypertension, dyslipidemia, or heart disease. No significant differences were observed on neuropsychological tasks between the groups for insulin treatment, obesity (overweight and normal), smoking (non/former smoker and current smoker) and consumption of alcohol (none/a few drinks per month and few drinks per week/daily). With regard to insulin treatment, patients with non insulin therapy (diet and oral hypoglycemic agents) had higher scores in the speed-related tasks, such as TMTA, VFT letter, and Digit Symbol, than the insulin therapy group, although these did not reach a significant level (TMTA, $P = 0.070$; VFT letter, $P = 0.123$, Digit Symbol, $P = 0.108$).

DISCUSSION

In the present study we investigated neuropsychological functioning in poorly controlled type 2 diabetes, controlled for factors that affect cognitive function. The diabetic patients showed a mild decrement in attention, working memory, verbal memory (story recall and word learning), processing speed, and executive function compared with the controls. No significant differences were observed between the two groups in word list recall (delayed and recognition) and visuospatial memory/visuoconstruction. Although ability of retained visuospatial memory and visuoconstruction are consistent with previous findings[6,7], poorly controlled diabetic patients displayed mild neuropsychological dysfunction in broader domains. When considering that the diabetic group had an equivalent MMSE score to the control group, and dementia was excluded from participants, the severity of cognitive impairment was very mild.

In a more detailed analysis of neuropsychological measures in middle-aged adults with type 2 diabetes, patients showed diminished performance in tasks that required speed within a fixed time such as TMTA, TMTB, Digit Symbol, and VFT. This psychomotor slowing was reported in middle-aged adults with type 2 diabetes[22]. As previously suggested, mental slowing might be a common manifestation of a 'central neuropathy' induced by chronic hyperglycemia. We failed to find a relation between any tasks of processing speed and metabolic control index. To assess whether the impaired processing speed is an intrinsic cognitive dysfunction of diabetes mellitus, and whether this impairment becomes prominent earlier than that for other neuropsychological functions, the longitudinal course of cognitive function with diabetes should be examined in a larger sample.

As another characteristic of neuropsychological data, patients with diabetes showed difficulties in story recall and word learning, whereas word recognition and delayed word recall were not impaired. Moreover, the Backward Digit Span was poorly performed. Both memory retrieval of story and Backward Digit Span require more cognitive resources and mental manipulation than word recognition and Forward Digit Span. In addition, recollecting a story from memory is a more complex task, where subjects are asked to retain considerable information in one hearing compared to remembering smaller speech units. Considering the result of unimpaired scores in trials 2–5 on word list recall among the diabetic population, dysfunction of verbal memory in patients with diabetes mellitus possibly may be more related to the attention component and working memory when verbal stimuli increase in complexity of structure and amount of information, rather than learning mechanisms.

In a previous study, hyperinsulinemia, elevated HbA1c, hypoglycemia, and peripheral neuropathy were shown to be related with cognitive decline in diabetic patients[23]. No relationship was found between the index of temporary glycemic control and neuropsychological measures in this study. Rather, in the diabetic group the aging effect was significant in several indices such as tasks requiring speed and executive function. As indicated in a previous review[24], age is an important risk factor in

cognitive impairment of diabetes mellitus. Interestingly, tasks related with attention-required executive function were not associated with age in the non diabetic group, whereas the tendency of processing speed decrement with advanced age was the same as the diabetic group. In normal aging, accelerated cognitive decline over the age of 50 was evident for speed and reasoning[25]. Moreover, learning abilities and short-term memory with task-required material diminished with aging[15]. Thus, attention and executive function might be accelerated by diabetic mechanisms as well as by aging. In the literature examining aging-related declines in relatively mild type 2 diabetes[10,11], significant group differences were present in speed-intensive measures of executive function and semantic speed across the two late life age groups (age 53–70 and age 71–90). This finding supports our hypothesis that the deteriorating attention and executive function with aging is a diabetes-related impairment. Backward Digit Span showed a relationship with the duration of diabetes. The duration of disease may reflect the cumulative influence of the disease, with the deficit of the Backward Digit Span representing diabetic-induced cognitive impairment. The hypothesis that decrement in attention, executive function, and working memory are characteristic of diabetes mellitus should be examined in a longitudinal design comparing groups having good and poor glycemic control.

Compared with previous literature examining cognitive dysfunction of type 2 diabetes of a similar age group[10,11], the diabetic participants in this study marked a significant lowering in the broader domains of neuropsychological measures. One possible reason for this is that the glycemic control of the diabetes group in the present study was poorer and that the rate of participants who were under treatment of insulin therapy was higher relative to previous studies. Although neither insulin treatment nor any other index of glycemic control associated with cognitive decrement, insulin and insulin receptors have been reported to be involved in learning and memory formation[26]. In addition, diabetic patients treated with insulin were at higher risk of dementia[27]. Several studies identified that insulin signaling may play a significant role in the pathophysiology of Alzheimer's Disease[28,29]. The long-term impact of insulin usage on brain mechanisms has to be investigated in a future study.

No relation was found between hypertension, dyslipidemia, obesity, or smoking and diminished neuropsychological functions. According to a systematic review, hypertension is the factor most consistently associated with cognitive decrements, whereas obesity and dyslipidemia are less consistently associated with them[30]. One study indicated a greater cognitive decline among people with comorbid diabetes and hypertension than among normotensive people with diabetes[31]. Because the average age of that study population at baseline was approximately 20 years older than that of our study group, the effect of age should be considered when interpreting the results. Another reason for the non significance is that our diabetic participants were treated with antihypertensive medications. Each antihyper-

tensive medication has different effects on the performance of neuropsychological functions[32]. Thus, the use of antihypertensive medication may affect the cognition of diabetic patients.

Finally, the diabetic group displayed significantly higher scores than the control group on the depression scale. Meta-analysis suggested that patients with type 2 diabetes had a twofold increased risk of depression compared with non diabetic subjects[33]. Although the scores ranged within the minimal level, which did not fulfill the diagnosis, diabetic patients had notably more depressive symptoms than non diabetic subjects.

In summary, diabetic patients with poor metabolic control showed mild cognitive dysfunction in a wide range of tasks related with working memory, processing speed, verbal memory, and executive function. The neuropsychological decline tended to be prominent when the tasks required more speed within a fixed time and when verbal stimuli became unstructured and complex. Accelerated aging had a major influence on cognitive decline in the diabetic group, whereas decrement in attention, executive function, and working memory might be more related to diabetes-related cognitive impairment. Because cross-sectional studies cannot capture cognitive decline over time, the neuropsychological characteristics should be analyzed in a longitudinal study with a wide range of age. Investigating the relationships between impaired neuropsychological measures and brain imaging is also necessary.

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