Risk factors of mild cognitive impairment in middle aged patients with type 2 diabetes: A cross–section study

Facteurs de risque du déficit cognitif léger chez les sujets d’âge moyen atteints de diabète de type 2 : une étude transversale

Rui-Hua Chen\textsuperscript{a}, Xiao-Zhen Jiang\textsuperscript{a, \textasteriskcentered}, Xiao-Hui Zhao\textsuperscript{b}, Yu-Lan Qin\textsuperscript{a}, Zhe Gu\textsuperscript{a}, Pei-Li Gu\textsuperscript{a}, Bin Zhou\textsuperscript{a}, Zhen-Hong Zhu\textsuperscript{a}, Lin-Yan Xu\textsuperscript{a}, Yu-Feng Zou\textsuperscript{a}

\textsuperscript{a} Department of Endocrinology, Pudong New Area People’s Hospital, Chuan Huan Nan Road No. 490, Shanghai, China
\textsuperscript{b} Department of Neurology, Pudong New Area People’s Hospital, Shanghai, China

Abstract

The aim of this study was to evaluate the risk factors of mild cognitive impairment (MCI) in middle-aged patients with type 2 diabetes (T2DM). Methods. – Montreal Cognitive Assessment (MoCA) was applied as cognition assessment implement. One hundred and fifty-seven middle-aged type 2 diabetic patients were enrolled in this cross–section study (age 40–69, mean age 55 ± 7). There were 93 patients with MCI (MoCA score < 26) in MCI group and 64 with normal cognitive function (MoCA score ≥ 26) in control group. Information of history of disease, family history, data of BMI, WHR, HbA1c, FINS, C-Peptide (C-P), SBP, DBP, blood lipid (TG, TC, LDL-C, HDL-C and carotid ultrasound (carotid intima–medial thickness [C-IMT], carotid resistance index [RI]) was collected. Results. – There were significant differences in the rate of patients with hypertension (40.63 vs. 58.06%, \(p = 0.026\)), duration of diabetes mellitus (3.09 ± 4.04 vs. 4.80 ± 4.94 y, \(p = 0.024\)), C-P (2.79 ± 1.09 ng/ml vs. 2.26 ± 1.00 ng/ml, \(p = 0.008\)), Max C-IMT (0.81 ± 0.15 mm vs. 0.91 ± 0.15 mm, \(p < 0.001\)), Min C-RI (0.71 ± 0.06 vs. 0.68 ± 0.06, \(p < 0.05\)), and no significant differences in the duration of hypertension and hyperlipidemia, BMI, WHR, HbA1c, SBP, DBP and blood lipid between control group and MCI group. MoCA scores were positively correlated with C-P (\(r = 0.252, p = 0.005\)), and negatively correlated with the history of hypertension (\(r = -0.244, P = 0.002\)), duration of DM (\(r = -0.161, P = 0.044\)), Max C-IMT (\(r = -0.253, P = 0.005\)) and Min C-RI (\(r = -0.183, P = 0.023\)). Multiple regression analysis showed that history of hypertension (Beta = -0.267, \(P = 0.002\)), C-P (Beta = 0.281, \(P = 0.001\)) and Min C-RI (Beta = -0.221, \(P = 0.011\)) were significantly independent determinants for the MoCA scores. Conclusions. – The longer duration of diabetes, history of hypertension, lower serum C-P levels, thickened C-IMT and higher C-RI could be risk factors of MCI in type 2 diabetic patients. This finding could have an important impact on the management of cognitive decline in diabetic patients.

© 2012 Elsevier Masson SAS. All rights reserved.

Résumé

L’objectif de cette étude est d’évaluer les facteurs de risque du déficit cognitif léger (mild cognitive impairment [MCI]) chez les sujets d’âge moyen atteints de diabète de type 2. Méthodes. – Mesure du niveau de dysfonction cognitive grâce à la cotation du Montreal Cognitive Assessment (MoCA). Étude transversale de 157 patients âgés de 40 à 69 ans (moyenne 55 ± 7) présentant un diabète de type 2. Il y avait 93 patients MCI (MoCA < 26) et un groupe contrôle de 64 patients sans dysfonction cognitive (MoCA ≥ 26). Paramètres étudiés : histoire de la maladie, antécédents familiaux, BMI, WHR, HbA1c, FINS, CRP, SBP, DBP, bilan lipidique (TG, TC, LDL-C, HDL-C, échographie carotidienne [mesure de l’épaisseur intima–média carotidienne [C-IMT] et de l’indice de résistance carotidienne [C-RI]) Résultats. – En comparant les sujets MCI au groupe contrôle, les résultats montraient des différences significatives pour les paramètres suivants : hypertension artérielle (40.63 % vs 58.06 %), \(p = 0.026\), durée de la maladie diabétique (3.09 ± 4.04 ans vs 4.80 ± 4.94 ans), \(p = 0.024\), CRP (2.79 ± 1.09 ng/ml vs. 2.26 ± 1.00 ng/ml), \(p = 0.008\), Max C-IMT (0.81 ± 0.15 mm vs. 0.91 ± 0.15 mm, \(p < 0.001\)), Min C-RI (0.71 ± 0.06 vs. 0.68 ± 0.06, \(p < 0.05\)). Aucune différence n’était retrouvée pour la durée de l’hypertension artérielle et l’hyperlipidémie, BMI, WHR, HbA1c, SBP, DBP et le bilan lipidique. Il y avait une corrélation positive entre le MoCA et le CRP (\(r = 0.252, p = 0.005\)) et une corrélation négative entre le MoCA et une histoire d’hypertension (\(r = -0.244, P = 0.002\)), durée du diabète (\(r = -0.161, P = 0.044\)), max C-IMT (\(r = -0.253, P = 0.005\)) et min C-RI (\(r = -0.183, P = 0.023\)). Selon l’analyse multifactorielle, une histoire d’hypertension (Bêta = -0.267, \(p = 0.002\)), CRP (Bêta = 0.281, \(p = 0.001\)) et min C-RI (Bêta = -0.221, \(p = 0.011\)) étaient des déterminants indépendants de la mesure de la dysfonction cognitive (MoCA). Conclusions. – Une durée plus longue de la maladie diabétique, une histoire...
d’hypertension, une CRP plasmatique basse, une épaisseur intima-média carotidienne et un indice de résistance carotidienne élevés seraient des facteurs indépendants du déficit cognitif léger chez les sujets présentant un diabète de type 2. Ces résultats pourraient avoir un impact important sur la prise en charge du déclin cognitif des diabétiques.

© 2012 Elsevier Masson SAS. Tous droits réservés.

1. Introduction

Type 2 diabetes (T2DM) is associated with many chronic complications including stroke and cardiovascular disease. In additional, diabetes may also contribute to the development of cognitive dysfunction [1,2]. It has been reported that T2DM is associated with decreases in psychomotor speed [3], verbal memory [4], immediate recall, delayed recall [5], and verbal fluency [5]. Research has been focusing on the study of mild cognitive impairment (MCI), which is an intermediate clinical condition between normal aging and dementia [6]. MCI is defined by an impairment of memory and other cognitive functions, not so serious as dementia [7].

In this cross-sectional study, we compare cases of MCI and normal controls (NC) of middle-aged diabetes adults in Pudong New Area People’s Hospital, Shanghai, China, in order to find out risk factors of MCI in such population.

2. Subjects and methods

2.1. Subjects

A cross-sectional study was conducted in patients with a history of T2DM recruited from the outpatient clinic of Endocrine department in Pudong New Area People’s Hospital. The study group comprised of 157 subjects belonging to both genders in the age group 40–69 years, and diabetes duration (0–20 years). The study group was divided into two groups (MCI Group: MoCA score < 26, n = 93, normal cognitive function (NC) group: MoCA score ≥ 26, n = 64). There were no significant differences in sex (male/female = 37/27 vs. 44/49, P > 0.05), mean age ([55.37 ± 7.15 years old vs. 55.33 ± 7.83 years old], P > 0.05) and years of education ([10.16 ± 3.07 vs. 9.21 ± 3.42 years] P > 0.05) in both groups. Data collection started in December 2010 and completed in November 2011. Cognitive evaluation was performed on all the subjects by using Montreal Cognitive Assessment (MoCA) Beijing version. All subjects had the ability to response the questionnaires and receive all the clinical and blood test and inclusion criteria of MCI group were as follows: Complaints of hypomnesis; MoCA score < 26; Clinical dementia rating (CDR) ≥ 0.5. Inclusion criteria of NC group was MoCA score ≥ 26. Exclusion criteria were as follows: those with diabetic ketoacidosis or other acute diabetic complications in recent 3 months, with severe heart failure, chronic renal failure, lung disease, or had the history of infection in central nervous system, stroke, cerebral hemorrhage or other clinical evidences of central nervous damages; persons with history of auditory disorders and psychological disturbances, which might interfere with the MoCA test; patients with history of chronic disease which could cause dementia (including Alzheimer syndrome, Parkinson syndrome, vascular dementia, Huntington’s disease, hydrocephalus, brain neoplasm, epilepsy, multiple sclerosis, chronic subdural hematoma, severe head trauma, abnormal brain structure, schizophrenia, etc.); history of alcohol abuse or drug abuse; history of depression and took antidepressants from 6 months before the recruitment; those who received medicines which can affect cognitive function 1 months before the study (e.g.: steroid, antiepileptic drug, sedative-hypnotic drug, anesthetics, etc.).

2.2. Methods

Demographic characteristics and medical history: datas were collected including age, gender, years of education, duration of diabetes, history and duration of hypertension and dyslipidemia, body mass index (BMI), waist hip ratio (WHR). Systolic blood pressures (SBP), diastolic blood pressure (DBP) were measured. Blood samples were obtained at fasting, Fasting glucose (FPG), triglyceride (TG), total cholesterol (TC), low-density cholesterol (LDL-C), high-density cholesterol (HDL-C) (Cobas 8000 C702 auto chemistry analyzer, Roche, enzyme method), HbA1c (HLC-723G7 analyzer, TOSOH kabushiki kaisha, HPLC), fasting insulin (FINS) and C-peptide (C-P) (Cobas 6000 analyzer, Roche, electrochemiluminescence immunoassay), were determined using standard laboratory procedures.

2.2.1. Cognitive measures

MoCA scale was applied to assess the cognitive situation of all subjects. Here we give a detailed introduction to MoCA Beijing version. The final English version of the MoCA is a one-page 30-point 10-minute screening test to identify elderly people with MCI [8]. The MoCA Beijing version used in this study is based on MoCA and contains some cultural and linguistic changes but carries the same meaning as the English version [9]. The instructions are:

- add an extra point if the individual has 12 years or fewer of formal education;
- operators need to give all patients similar commands as far as possible to reduce errors and ensure that subjects do not get any hint from the commands;
- and control operating time strictly. In order to reduce the experimental error, the results are excluded if the completion time of the MoCA is longer than 20 minutes. Patients with scores less than 26 were determined as MCI.

2.2.2. Ultrasonography of carotid arteries

Detailed B-mode images of the right and left common carotid artery (CCA), carotid bifurcation, and the first 1.5 cm of the internal carotid artery (ICA) were obtained at each ultrasound visit using a Sequoia scanner (SIEMENS, Germany) equipped with a 4–6 MHz linear array imaging probe. IMT and resistance index...
Demographics in NC group and MCI group.

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>MCI</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>64 (37/27)</td>
<td>93 (44/49)</td>
<td>2.549</td>
<td>0.280</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>55.06 ± 7.28</td>
<td>55.34 ± 8.35</td>
<td>−0.218</td>
<td>0.827</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.16 ± 3.07</td>
<td>9.21 ± 3.42</td>
<td>1.631</td>
<td>0.105</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>26 (40.63%)</td>
<td>64 (58.06%)</td>
<td>4.933</td>
<td>0.026</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>43 (67.19%)</td>
<td>61 (65.59%)</td>
<td>0.043</td>
<td>0.835</td>
</tr>
<tr>
<td>Family history of T2DM</td>
<td>21 (32.81%)</td>
<td>35 (37.63%)</td>
<td>0.384</td>
<td>0.535</td>
</tr>
<tr>
<td>Duration of hypertension (y)</td>
<td>3.26 ± 7.00</td>
<td>4.10 ± 5.54</td>
<td>−0.842</td>
<td>0.401</td>
</tr>
<tr>
<td>Duration of hyperlipidemia (y)</td>
<td>0.94 ± 1.72</td>
<td>1.40 ± 3.61</td>
<td>−0.949</td>
<td>0.344</td>
</tr>
<tr>
<td>Duration of T2DM (y)</td>
<td>3.09 ± 4.04</td>
<td>4.80 ± 4.94</td>
<td>−2.287</td>
<td>0.024</td>
</tr>
</tbody>
</table>

NC: normal cognitive function; MCI: mild cognitive impairment.

RI (RI) of both sides of CCA were recorded. To measure the average IMT of each segment, lines were electronically drawn along 1-cm segments of the lumen-intima interface and the media-adventitia interface of the near and far walls of the distal CCA and along the far walls of the carotid bulb and ICA. The average of this was recorded for each location. The mean of all average readings across the eight locations (four on each side) was calculated. The site of the greatest thickness including a plaque lesion was sought along both near and far walls bilaterally (max-IMT). The RI was calculated by subtracting end-diastolic Doppler-shifted frequency from peak-systolic-shifted frequency and dividing this value by peak-systolic-shifted frequency. Data of RI in both sides was classified into max and min RI.

### 3. Statistical analyses

All continuous data were tested for normality with Kolmogorov-Smirnov (KS) test. Statistical analysis was performed for comparison between groups (variables) with Independent t-test (normally distributed) and Mann-Whitney U test (non-normally distributed) for continuous data. The Chi² test was used for comparison of categorical variables. Series of Pearson correlation and Spearman rank correlation methods were used to determine the variables that correlated with MoCA. Multiple linear regression was used to create a prediction model for correlations of variables and MoCA scores. These analyses were performed using the Statistical Package for the Social Science (SPSS Graduate Student Version 16.0 for Windows). A P-value of less than 0.05 was considered to be significant.

### 4. Results

Leamer correlation analysis showed that sex (r = −0.092, P = 0.198) and age (r = −0.048, P = 0.550) were not associated with MoCA scores in these subjects. So the difference of cognitive function induced by sex and age was excluded in this study. Comparing with the NC group, the incidence of hypertension was higher in MCI group (58.06% vs. 40.63%, P = 0.026). The durations of diabetes were longer in MCI group than in NC group (4.80 ± 4.94 y vs. 3.09 ± 4.04 y, P = 0.024) (Table 1). No significant differences were found between the two groups in the incidence of hyperlipidemia, family history of diabetes, the durations of hypertension and hyperlipidemia. Lower C-P levels were observed in MCI group (2.63 ± 1.00 ng/ml vs. 2.79 ± 1.09 ng/ml, P = 0.008). No significant differences were found in BMI, WHR, FPG, HbA1c, SBP, DBP, TG, TC, HDL-C, LDL-C (Table 2).

Ultrasonography of carotid arteries showed an increase of IMT in both sides (left: 0.87 ± 0.16 vs. 0.79 ± 0.14, P < 0.001; right: 0.87 ± 0.16 vs. 0.77 ± 0.16, P = 0.001) and max-IMT (0.91 ± 0.15 vs. 0.81 ± 0.15, P < 0.001) in MCI group. An increase in min-RI (0.71 ± 0.06 vs. 0.68 ± 0.06, P = 0.030) was also found in MCI group (Table 2).

We evaluated the relationships between MoCA scores and the duration of diabetes, history of hypertension, levels of C-P, max-IMT and min-RI. A positive correlation was observed between MoCA scores and C-P (r = 0.252, P = 0.005). MoCA scores was negatively correlated with the history of hypertension (r = −0.244, P = 0.002), duration of DM (r = −0.161, P = 0.044), max-IMT (r = −0.253, P = 0.005) and min-RI (r = −0.183, P = 0.023). On multiple regression analysis to which MoCA scores as a dependent variable, and the duration of diabetes, history of hypertension, levels of C-P, max-IMT and min-RI as operands were included as independent variables. The significant relationship between MoCA scores and duration of hypertension (β = −0.267, P = 0.002) and C-P levels (β = 0.281, P = 0.001), as well as between MoCA scores and min-RI (β = −0.221, P = 0.011) was found.

### 5. Discussion

MCI is a syndrome defined as cognitive decline greater than expected for an individual’s age and education level but that does not interfere notably with activities of daily life. It is, thus,
distinct from dementia, in which cognitive deficits are more severe and widespread and have a substantial effect on daily function [10]. Many studies have reported cognitive deficits in type 2 diabetics when compared to a non-diabetic population [11,12]. Some studies showed that the incidence of cognitive impairment was higher in patients with T2DM than non-diabetic subjects [4,13]. About 10.8% of the subjects with MCI in patients with T2DM.

The mechanism responsible for cognitive decline associated with diabetes was still unclear. A number of possible mechanisms have been raised. Firstly, hyperglycemia appears to be related to abnormalities in cognitive function in patients with T2DM [17]. In other studies, hyperinsulinemia [18] was supposed to be another risk. At present study, we found cognitive function was not associated with duration of hypertension and hyperlipidemia, history of hyperlipidemia, BMI, WHR, levels of FPG, HbA1c, FINS, SBP, DBP, TG, TC, HDL-C or LDL-C. But we demonstrated several risk factors possibly associated with MCI in patients with T2DM.

We found DM duration was important in the pathogenesis of cognitive impairment. Durations of DM in MCI group were longer than in NC group. Pearson analysis showed reverse relationship between duration of DM and MoCA scores. This finding was in agreement with other studies, which reported the correlation between duration of DM and cognitive function [19,20].

A greater decline among the hypertensive diabetes patients would have been expected. We found that the incidence of hypertension was higher in MCI group than NC group (58.06% vs. 40.63%, $P = 0.026$). Spearman analysis and multiple regression showed that history of hypertension was correlated with cognitive impairment. This finding confirms other data [21,22]. We didn’t find the relationship between MoCA score and SBP or DBP. We speculated that may be caused by the effect of hypotensor.

Macrovascular (including cardiovascular, cerebrovascular and peripheral vascular) atherosclerosis was considered as the most common complications caused by diabetes. Patients with diabetes were more likely to have chronic cerebrovascular disease comparing to the control group [13]. In Thus, a relationship between cognitive changes and diabetes may be based on progression of cerebrovascular disease. Many study proved that IMT was a common marker of atherosclerosis [23]. Recently, Gaetano et al. [24] revealed that IMT was also associated with cognitive function. In our study, Mean IMT of MCI group was higher than that of NC group, indicating that atherosclerosis did make contribution to cognitive function in this population. We also found RI, especially minimum RI in MCI group was greater than NC group, and was associated with MoCA scores. RI was introduced by Pourcelot [25] in 1974, to detect peripheral vascular disease. It is calculated from blood flow velocities in vessels during the cardiac cycle by a pulsed-wave Doppler ultrasound, and could represent the stiffness and resistance of carotid vessel. The higher the values, the greater is the impedance to blood flow. Previous studies showed RI was closely related to atherosclerosis and CVD [26]. Our study revealed that min RI was positively correlated with duration of DM ($r = 0.363, P < 0.001$) and max IMT ($r = 0.363, P < 0.001$) but not history ($r = 0.132, P = 0.104$) or duration of hypertension ($r = 0.138, P = 0.089$), suggested that min RI of patients in this study was associated with DM and atherosclerosis but not hypertension. Although no else study indicated relationship between RI and cognitive function, we still conjectured that stiffness of artery increases and atherosclerosis intensifies along with diabetic course prolonging, which contribute to the increase of arterial RI and decrease of blood flow of brain. All above would cause hypoxic ischemia of cerebral and MCI ultimately.

We found low level of serum C-P as a potential risk factor of MCI in this study by comparing all the demographic characteristics. C-P is a 31–amino acid peptide that is cleaved from proinsulin during biosynthesis of insulin [27]. Recent studies have shown that C-P possesses physiological functions other than providing structural support for proinsulin cleavage. C-P improves renal function, reduces urinary albumin excretion and glomerular filtration, and decreases blood retinal barrier leakage [28]. Although Olivia et al. [29] thought Higher levels of C-P in those without diabetes was related to decline in general cognition and verbal memory, some other study [30] found C-P replacement prevented oxidative stress, endoplasmic reticulum, nerve growth factor receptor p75, and poly (ADP-ribose) polymerase-related apoptotic activities, thus, prevent the cognitive dysfunction in type 1 DM. Our study showed C-P level was lower in MCI group than NC group, and were positively correlated with MoCA scores, indicating that patients with higher level of C-P keeps more cognitive function. Whereas patients with shorter duration of DM were with high insulin secretion and C-P level, whether the result was caused by C-P’s own physiological function or bias by duration of DM is unclear. Further study is needed to find out the relationship and mechanism between them.

Unlike some other study, we didn’t find any directly correlations of cognitive function with blood glucose, blood pressure, blood lipids. We speculated the causes were as follow: some patients with high MoCA score and high blood glucose were new diagnosed, which were with short duration of DM; patients were with different recognition of their own disease condition and underwent different therapies; subjects in our study had different age range from other studies, which maybe with different level of cognitive function.

Our study has a number of limitations. Firstly, patients recruited in this study received different therapy that we didn’t exclude the effect of medication to the cognitive function. Next, our findings of negative relationships may be a consequence...
of having evaluated individuals with modest cognitive deficits who had few co-morbid conditions and were in relatively good metabolic control at study entry. Furthermore, the data collection of some factors including duration of DM, hypertension, hyperlipidemia and family history were on self-report and the medical record which may have lead to recall bias. Furthermore, sample in this study was not larger enough to represent all diabetic patients. However, this sample size was considered to be sufficiently powered to examine the relationship between C-P levels, macrovascular complications and cognition in diabetic patients.

In summery, we found that duration of DM, history of hypertension, low serum C-P level and subclinical macrovascular complications including thickened C-IMT and higher C-RI were closely associated with MCI in patients with T2DM. We supposed this finding could have an important impact on the management of cognitive decline in diabetic patients. Further confirmation of the association is required in enlargement of the number of samples and the form of a randomized, controlled trial of intensive versus less intensive glycemic control with cognitive endpoints.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

This work was supported by a joint research project of Shanghai health bureau (2009214) and science committee of Shanghai Pudong New Area (PKJ2010-Y25).

References
