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Relationship between olfactory dysfunction and cognitive impairment in elderly patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Recent clinical studies identified the relation between olfactory dysfunction and cognitive impairment in the elderly without type 2 diabetes mellitus. The aim of the present study was to define the relation between olfactory function and cognition in elderly patients with type 2 diabetes mellitus.

Methods: The study participants comprised 250 elderly (age, 68–77, median 72) Japanese outpatient with type 2 diabetes mellitus free of clinically-evident cognitive impairment. Olfactory and cognitive functions were evaluated by the Open Essence (OE) test and Mini-mental State Examination (MMSE), respectively.

Results: Based on the MMSE score, 62.0%, 24.4%, and 13.6% of the participants were considered to have no impairment, possible cognitive impairment and probable dementia, respectively. The OE test score of the probable dementia group was significantly lower than other groups. Furthermore, age and serum uric acid were significantly higher in the probable dementia group than other groups. Simple correlation analysis showed positive correlation between the MMSE score and diastolic blood pressure, education, OE test score, total

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Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; AST, aspartate aminotransferase; BDI, Beck Depression inventory; BMI, body mass index; HDL, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MCI, mild cognitive impairment; MMSE, Mini-mental State Examination; OE, Open Essence; UAE, Urinary albumin excretion.

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cholesterol, LDL cholesterol, folic acid, and negative correlation with age, HbA_{1c}, aspartate aminotransferase, serum adiponectin and urinary albumin excretion. Multivariate regression analysis showed that OE test score correlated significantly and independently with MMSE score (standardized coefficients $\beta = 0.542$, $R^2 = 0.478$, $P < 0.01$), in addition to education level, HbA_{1c} and serum adiponectin.

Conclusions: The results suggested the association of olfactory dysfunction with cognitive impairment in elderly patients with type 2 diabetes mellitus.

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1. Introduction

One of the main objectives of treatment of type 2 diabetes mellitus is to reduce the onset and development of diabetes-related complications [1]. To achieve these goals, diabetes treatment regimens have been continuously revised. However, self-care management is always an integral part of the overall management of type 2 diabetes mellitus.

Patients with type 2 diabetes mellitus are about two to four times more likely to develop cognitive impairment and dementia than individuals without type 2 diabetes mellitus [2]. Such impairment can potentially affect diabetes self-care and adherence to medication, with consequent deterioration of glycemic control [3,4]. In terms of management of type 2 diabetes mellitus, it is crucial to prevent the development of cognitive impairment at an early stage or halt its progression. In this regard, it is important to identify makers for early cognitive impairment in patients with type 2 diabetes mellitus.

Several studies have demonstrated that olfactory dysfunction appears to precede clinical signs of Alzheimer's disease (AD) or cognitive impairment and may be an early marker of brain changes. Early studies related olfactory dysfunction with neurodegenerative diseases such as AD and Parkinson's disease [5,6]. Furthermore, olfactory dysfunction was also reported in subjects with mild cognitive impairment (MCI) [7], as well as those with the apolipoprotein E epsilon 4 allele, a strong genetic risk factor for AD [8], and those with family history of AD [9]. Recent clinical studies also identified the relation between olfactory dysfunction and cognitive impairment in the elderly [10,11]. In addition, patients with olfactory dysfunction were more likely to make the transition to clinical AD than those without [7]. Taken together, these studies suggest that olfactory function is not only associated with cognitive function, but also could be used as an early marker of future cognitive impairment and AD.

Impaired olfactory function has also been reported in patients with type 2 diabetes mellitus [12]. However, similar to general population, whether olfactory dysfunction is related to cognitive impairment and/or could be an early marker of future cognitive impairment in patients with type 2 diabetes mellitus remains unknown. As a first step, we investigated the relationship between olfactory dysfunction and cognitive impairment in elderly patients with type 2 diabetes mellitus who showed no clinical evidence of cognitive impairment.

2. Materials and methods

2.1. Subjects

Patients with type 2 diabetes mellitus who met the eligibility criteria described below were invited to participate in the present study through the Diabetes Outpatient Clinic of Juntendo University Hospital (Tokyo, Japan) and Juntendo Tokyo Koto Geriatric Medical Center (Tokyo, Japan). The eligibility criteria were patients with type 2 diabetes mellitus aged more than 65 years with free of clinically-evident cognitive impairment. The exclusion criteria were (1) patients with severe infections within the preceding 2 weeks, (2) patients scheduled for surgery or who had undergone surgery, (3) patients with severe trauma, (4) patients with psychiatric disorders, (5) patients with hypothyroidism, (6) patients with partial or complete olfactory dysfunction associated with sinusitis, allergic rhinitis, and deviated nasal septum, (7) patients with history of brain tumors, (8) patients on steroid treatment, (9) patients with a Mini-mental State Examination (MMSE) score of less than 18 points [they were considered to have severe and moderate cognitive impairment [13]], and (10) patients who were considered ineligible based on the assessment of clinical investigators. Among 312 consecutive elderly patients with type 2 diabetes mellitus who were screened, 256 patients met the above criteria. After being informed of the purpose and procedures of the study, olfaction and cognitive tests were performed between October 2012 and December 2013. Among the 256 patients, three with MMSE score of less than 18 points were diagnosed with severe or moderate cognitive deficit for the first time [13] and were excluded from the study. Following blood sampling and laboratory test, three patients were found to have hypothyroidism and were also excluded from the study. The remaining 250 patients were the subjects of this cross-sectional study. The study protocol was approved by the Institutional Review Board of Juntendo University Hospital and the study was conducted in accordance with the principles described in the Declaration of Helsinki. All patients provided written informed consent before enrolment in the study. The study has been registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000011073).

2.2. MMSE

Cognitive status was evaluated by the MMSE [14]. The MMSE is widely used for the assessment of cognitive status in both

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