eNeurologicalSci 8 (2017) 9–10

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Letter to the Editor

Cerebrospinal fluid analysis in individuals with diabetes-related dementia

Dear Editor,

Type 2 diabetes mellitus (DM) has been shown to be a risk factor for the development of Alzheimer's disease (AD) and vascular dementia (VaD). In addition to AD and VaD, there may be a dementia subgroup associated with specific DM-related factors rather than with AD pathology or vascular diseases. This type of dementia, not showing hypoperfusion in the parietotemporal lobe on single photon emission CT or cerebrovascular lesions on magnetic resonance imaging, is characterized by high hemoglobin A_{1c} level, long duration of diabetes, high frequency of insulin therapy, low frequency of apolipoprotein E4 carrier, less severe medial temporal lobe atrophy, impaired attention and executive function, less impaired word recall, and slow progression of cognitive impairment, and might be referred to as diabetes-related dementia [1,2]. This subtype of dementia accounts for at least 10% of all patients with dementia associated with DM. They often showed negative or equivocal amyloid accumulation in the brain on ^{11}C-Pittsburgh compound-B (PiB) positron emission tomography (PET) [2]. These findings suggest that underlying neuropathology in diabetes-related dementia is not associated with AD pathologic changes, particularly amyloid pathology. In the present study, we analyzed cerebrospinal fluid (CSF) in individuals with diabetes-related dementia and those with AD and compared levels of phosphorylated tau (P-tau), β-amyloid 40 (Aβ40), and β-amyloid 42 (Aβ42).

The study included 11 subjects with diabetes-related dementia, 39 with probable AD, and 18 with non-dementia neurological diseases (control group). The diagnosis of diabetes-related dementia was based on our proposed guidelines for the clinical diagnosis of diabetes-related dementia [3]. The subjects with AD had to meet the National Institute on Aging and Alzheimer's Association (NIA/AA) criteria for a diagnosis of probable AD [4]. All patients underwent general physical examinations, clinical neurological examinations, laboratory tests, and brain imaging studies to exclude other potential causes of dementia. Non-dementia neurological diseases include cervical spondylosis, migraine, depression, and hydrocephalus without cognitive impairment. The CSF findings were not used for any diagnosis in this study. The CSF samples were collected by lumbar puncture and were analyzed using commercially available enzyme-linked immunosorbent assays (ELISA) to determine the levels of P-tau, Aβ40, and Aβ42. The methods were previously described in detail [5]. Values were expressed as the mean ± SD. Statistical analysis was performed using one-way analysis of variance (ANOVA) with the post hoc Fisher's Protected Least Significant Difference (PLSD) test and the χ^2 test. Written informed consent was obtained from all subjects or their relatives. This study was approved by the ethics committee of Tokyo Medical University.

There were no significant differences in age (78.8 ± 10.3 years in controls, 81.2 ± 7.5 years in diabetes-related dementia, and 77.9 ± 7.6 years in AD), gender (8 men and 10 women in controls, 3 men and 8 women in diabetes-related dementia, and 16 men and 23 women in AD), and education (13.1 ± 4.2 years in controls, 13.2 ± 3.0 years in diabetes-related dementia, and 12.7 ± 2.5 years in AD) among the three groups. MMSE scores in the AD group and the diabetes-related dementia group were significantly lower than those in the control group (26.6 ± 4.3 in controls, 21.8 ± 3.1 in diabetes-related dementia, and 20.3 ± 5.1 in AD; control vs. diabetes-related dementia, $p < 0.0001$; control vs. AD, $p < 0.0001$), but no significant differences in MMSE scores and duration of dementia were found between the AD group and the diabetes-related dementia group (3.4 ± 1.0 years in diabetes-related dementia and 3.5 ± 1.5 years in AD). Fig. 1 shows CSF P-tau, Aβ40, and Aβ42 levels among the three groups. CSF P-tau levels were significantly higher in the AD group than in the control group and the diabetes-related dementia group. P-tau levels in the diabetes-related dementia group were in-between the AD group and the control group, but showed no significant differences between the control group and the diabetes-related dementia group. Although there were no significant differences in Aβ40 levels among the groups, Aβ42 levels were significantly lower in the AD group than in the control group and the diabetes-related dementia group. No significant differences in Aβ40 and Aβ42 levels were found between the diabetes-related dementia group and the control group.

The combination of high P-tau and low Aβ42 levels in the CSF can predict the presence of AD pathology with high accuracy [6]. We found that individuals with diabetes-related dementia showed different P-tau and Aβ42 levels from those with AD. These findings suggest that diabetes-related dementia involves different pathophysiology from AD histopathological features. Diabetes-related dementia is not suggestive of a particular underlying neuropathology, but merely describes a dementia state predominantly associated with DM-related metabolic abnormalities rather than AD or vascular pathology. Therefore, diabetes-related dementia seems to be a heterogeneous disease. In our preliminary tau PET study, most patients with diabetes-related dementia showed accumulation of ^{11}C-pyridinyl-butadienyl-benzothiazole 3 (PBB3) [7] in the brain, including the medial temporal lobe, suggesting tau deposition in the brain (unpublished data). Although we have no autopsy data, diabetes-related dementia may be associated with tauopathy, such as senile dementia of the neurofibrillary tangle type [8] or primary age-related tauopathy (PART) [9], and non-specific neuronal damage due to glucose toxicity. The present CSF study seems to be consistent with our amyloid and tau PET findings. Subjects with diabetes-related dementia have often been misdiagnosed as having AD. However, this type of dementia is apparently different from AD in terms of clinical features, clinical course, underlying pathophysiology, treatment, and care. Although the control group includes some patients with neurological diseases affecting CSF findings, we conclude that CSF analysis may be useful for the differentiation of diabetes-related dementia from AD. Further studies with pathological confirmation are needed to confirm our results.

http://dx.doi.org/10.1016/j.ensci.2017.06.002
Received 12 June 2017; Accepted 12 June 2017
Available online 13 June 2017

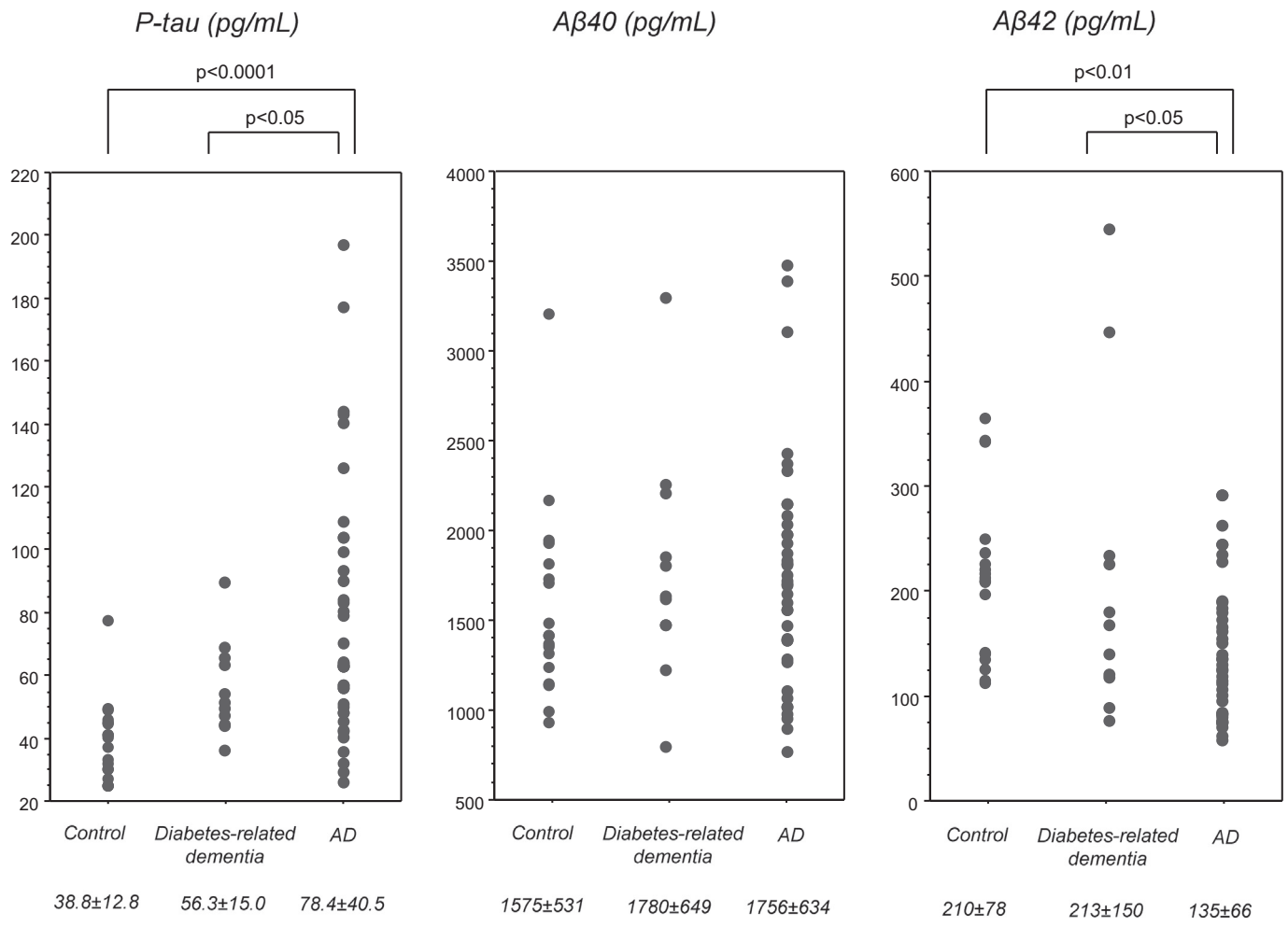

Fig. 1. P-tau, Aβ40, and Aβ42 levels among the three groups.

Disclosure statement

The authors have indicated no financial support.

Conflicts of interest

There are no conflicts of interest related to this study.

Acknowledgements

We are grateful to the medical editors from the Department of International Medical Communications of Tokyo Medical University for editing and reviewing the English manuscript. This work was supported by a JSPS KAKENHI Grant-in-Aid for Scientific Research (c) No. 15K09326.

References

[1] R. Fukazawa, H. Hanyu, T. Sato, et al., Subgroups of Alzheimer's disease associated with diabetes mellitus based on brain imaging, Dement. Geriatr. Cogn. Disord. 35 (2013) 280–290.
[2] R. Fukasawa, H. Hanyu, S. Shimizu, et al., Identification of diabetes-related dementia: longitudinal perfusion SPECT and amyloid PET studies, J. Neurol. Sci. 349 (2015) 45–51.
[3] H. Hanyu, D. Hirose, R. Fukasawa, et al., Guidelines for the clinical diagnosis of diabetes mellitus-related dementia, J. Am. Geriatr. Soc. 63 (2015) 1721–1722.
[4] G.M. McKhann, D.S. Knopman, H. Chertkow, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup, Alzheimers Dement. 7 (2011) 263–269.
[5] M. Shoji, E. Matsubara, M. Kanai, et al., Combination assay of CSF tau, Aβ1-40 and Aβ1-42(43) as a biochemical marker of Alzheimer's disease, J. Neurol. Sci. 158 (1998) 134–140.
[6] T. Tapiola, I. Alafuzoff, S.K. Herukka, et al., Cerebrospinal fluid β-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain, Arch. Neurol. 66 (2009) 382–389.
[7] M. Maruyama, H. Shimada, T. Suhara, et al., Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls, Neuron 79 (2013) 1094–1108.
[8] M. Yamada, Senile dementia of the neurofibrillary tangle type (tangle-only dementia): neuropathological criteria and clinical guidelines for diagnosis, Neuropathology 23 (2003) 311–317.
[9] J.F. Crary, J.Q. Trojanowski, J.A. Schneider, et al., Primary age-related tauopathy (PART): a common pathology associated with human aging, Acta Neuropathol. 128 (2014) 755–766.

Hidekazu Kanetaka, Raita Fukasawa, Soichiro Shimizu, Naohito Takenoshita, Haruo Hanyu
Department of Geriatric Medicine, Tokyo Medical University, Japan
E-mail address: hidekazu@xg7.so-net.ne.jp

* Corresponding author.