Spicy food consumption is associated with cognition and cerebrospinal fluid biomarkers of Alzheimer disease

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Abstract
Background: Recent studies suggest that a healthy diet helps to prevent the development of Alzheimer disease (AD). This study aimed to investigate whether spicy food consumption is associated with cognition and cerebrospinal fluid (CSF) biomarkers of AD in the Chinese population.

Methods: We enrolled 55 AD patients and 55 age- and gender-matched cognitively normal (CN) subjects in a case-control study, as well as a cohort of 131 participants without subjective cognitive decline (non-AD) in a cross-sectional study. Spicy food consumption was assessed using the Food Frequency Questionnaire (FFQ). Associations of FFQ scores with cognition and CSF biomarkers of AD were analyzed.

Results: In the case-control study, spicy food consumption was lower in AD patients than that in CNs (4.0 [4.0–8.0] vs. 8.0 [4.5–10.0], P < 0.001); FFQ scores were positively associated with Mini-Mental Status Examination scores in the total sample (r = 0.218, P = 0.014). In the cross-sectional study, the association between spicy food consumption and cognition levels was verified in non-AD subjects (r = 0.264, P = 0.0023). Moreover, higher FFQ scores were significantly associated with higher β-Amyloid (1–42) (Aβ42) levels and lower phospho-tau/Aβ42 and total tau/Aβ42 ratios in the CSF of non-AD subjects (P < 0.05).

Conclusion: Spicy food consumption is closely related to higher cognition levels and reversed AD biomarkers in the CSF, suggesting that a capsaicin-rich diet might have the potential to modify the cognitive status and cerebral pathologies associated with AD.

Keywords: Alzheimer disease; Biomarker; Capsaicin; Cerebrospinal fluid; Cognition; Spicy food

Introduction
Alzheimer disease (AD) is the most common cause of age-related dementia among the elderly population. To date, no effective therapy has been available to halt the progression of AD. Due to the failures of clinical trials in patients with advanced AD, the intervention for AD has shifted from treatment to prevention in at-risk populations. Recent studies suggest that a healthy diet helps to prevent the development of AD.

Spicy food is popular in many regions of China. Capsaicin is the major component in chili peppers, accounting for the spicy/pungent flavor. It is interesting to note that there is a geographic overlap between AD incidence and spicy food consumption in China. The incidence of AD in western China (3.99/1000 person-years) is lower than that in eastern China (5.58/1000 person-years), while the proportion of dishes containing chillis is higher and the pungency degree is greater in western China than those in eastern China. Previously, we reported that capsaicin-rich diet consumption was associated with better cognition and lower blood β-Amyloid (AB) levels in subjects aged 40 years and older. These findings imply that a capsaicin-rich diet may be protective against AD. In the present study, we further investigated the association of spicy food consumption with cognition and AD biomarkers in cerebrospinal fluid (CSF) in the Chinese population.

Methods
Ethical approval
This study was approved by the Institutional Review Board at the Daping Hospital and Qingdao Municipal Hospital.
and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from participants or their guardians.

**Study subjects and clinical assessment**

In the case-control study, 55 AD patients and 55 age- and gender-matched cognitively normal (CN) Chinese were recruited from the Daping Hospital from March to December 2018. The diagnosis of AD was defined by at least two neurologists in accordance with the “probable AD” criteria of the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer Disease and Related Disorders Association. Subjects were excluded for the following reasons: (1) a family history of dementia; (2) neurologic diseases such as hydrocephalus, Parkinson disease, epilepsy, inflammatory demyelinating diseases, stroke, brain trauma, and tumor; (3) other disorders that have the potential to affect CSF biomarker levels, including intracranial infections, intracranial hypertension, and hydrocephalus; (4) severe cardiac, pulmonary, hepatic, renal or hematological diseases, or malignant tumor; (5) enduring mental illness (eg, schizophrenia); and (6) inability to comply with the study assessment or refusal to participate.

The clinical evaluation of AD patients was performed according to our previous protocol. Demographic data (including age, sex, and educational level) and medical history were collected. Fasting blood was sampled for the examination of routine blood tests, electrolytes, liver and kidney function, coagulation function, thyroid function, vitamin B12, pre-transfusion examination (human immunodeficiency virus, syphilis, and hepatitis C), and tumor markers. The cognitive and functional status were first assessed with the Mini-Mental Status Examination (MMSE) and Activities of Daily Living Scale. If the participant had abnormal cognitive status, other cognitive tests were evaluated, including the Auditory Verbal Learning Test, clock drawing test, Trail Making Test, Boston naming test, digit span test, Clinical Dementia Rating, Pfeiffer Outpatient Disability Questionnaire, and Hachinski Ischemic Score.

In the cross-sectional study, a total of 131 participants without memory complaints (non-AD) were enrolled from the Daping Hospital (n = 62) and the Qingdao Municipal Hospital (n = 69) from March to December 2018. These non-AD participants suffered from urinary diseases and planned to undergo surgery with lumbar anesthesia. Neuropsychological assessments and the Food Frequency Questionnaire (FFQ) were conducted the day before the surgery. CSF was collected after lumbar anesthesia at the beginning of surgery.

**Assessment of spicy food consumption**

Consumption of spicy food during the last 12 months was assessed with FFQ, which includes four questions: (Q1) the degree of spicy food intake (no, mild, middle, or heavy); (Q2) the degree of food spiciness (no, mild, middle, or heavy); (Q3) the frequency of spicy food intake (less than once a week, approximately once a week, 2–6 times per week, or daily); and (Q4) the amount of spicy food intake (no, mild, middle, or heavy). The score for each question ranged from 1 (no) to 4 (heavy) points, and scores for all these questions were summed to obtain the total FFQ score, which could range from 4 to 16 points.

**CSF collection**

Lumbar punctures were conducted under local anesthesia. CSF was sampled and centrifuged within 2 h after collection at 2000 × g for 10 min at room temperature to eliminate cells and insoluble components, then aliquoted and stored at −80°C until use.

**Measurement of β-amyloid (1–40) (Aβ40), β-amyloid (1–42) (Aβ42), total-tau (t-tau), and phospho-tau181 (p-tau181)**

Levels of Aβ40, Aβ42, t-tau, and p-tau181 in CSF were measured using the following enzyme-linked immunosorbent assay kits: INNOTEST Aβ42, INNOTEST Aβ40, INNOTEST kTAU Ag t-tau, and INNOTEST p-tau181 (Innogenetics, Belgium).

**Statistics**

Continuous variables normally distributed are shown as mean ± standard deviation; those not normally distributed are presented as the median and interquartile range (25th–75th percentiles). Categorical variables are expressed as number (%). Statistical comparisons between the AD and CN groups were made using Student’s t test or Mann-Whitney U test as applicable for continuous variables and χ² test for categorical variables. Normality and equal-variance tests were performed for all assays. Since FFQ scores and several parameters were not normally distributed even after transformed or standardized, Spearman rank coefficients and partial correlation coefficients were used to analyze the correlations of FFQ scores with MMSE scores and CSF biomarkers, with adjustment for age, gender, and education which are important variates for cognition. Two-tailed P values < 0.05 were considered significant. All analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Characteristics of the study subjects**

The basic information of the AD patients and CNs in the case-control study is shown in Table 1. AD patients had lower MMSE scores (14.0 [5.5–18.5] vs. 28.0 [27.0–29.0], P < 0.001), years of education (6.0 [6.0–9.0] vs. 12.0 [9.0–12.0], P < 0.001), and FFQ scores (4.0 [4.0–8.0] vs. 8.0 [4.5–10.0], P < 0.001) than CNs.

**Association between spicy food consumption and cognition**

In the cohort containing AD patients and CNs, FFQ scores were positively associated with MMSE scores (r = 0.218, P = 0.014) after adjusting for education [Figure 1A]. In the cohort of non-AD participants, FFQ scores were also associated with MMSE scores (r = 0.264, P = 0.0023) after
adjusting for education and region [Figure 1B]. These findings suggest that consumption of spicy food may protect against cognitive decline.

**Associations between spicy food consumption and AD biomarkers in CSF**

Next, we investigated the association between spicy food consumption and AD biomarkers in the CSF of non-AD participants [Table 2]. FFQ scores were positively associated with the Aβ42 levels but negatively associated with p-tau181/Aβ42 and t-tau/Aβ42 ratios in CSF. After adjustment for age, sex, and education, FFQ scores were also associated with Aβ42 levels, p-tau181/Aβ42, and t-tau/Aβ42 ratios in CSF. Since ratios of t-tau/Aβ42 and p-tau/Aβ42 in CSF best discriminated Pittsburgh compound-B (PiB)-positive from PiB-negative individuals,[13] these findings imply that spicy food consumption may affect amyloid pathologies and neurodegeneration.

**Discussion**

In the present study, we found that spicy food consumption was lower in AD patients than that in CNs. In non-AD participants, spicy food consumption was correlated with MMSE scores and the AD core biomarkers Aβ42, p-tau181/Aβ42 ratio, and t-tau/Aβ42 ratio in CSF. These findings imply that a capsaicin-rich diet might offer protective effects against cognitive decline and AD-type pathologies.

Our previous study found that a capsaicin-rich diet was related to cognition and blood biomarkers in subjects aged 40 years and older.[10] In the present study, we further showed that a capsaicin-rich diet was associated with cerebral AD core biomarkers. Moreover, recent animal studies from our and other groups suggested that consumption of capsaicin was able to reduce brain Aβ pathology, attenuate neurodegeneration, and improve cognition in AD transgenic animals.[14,15] Taken together, our findings suggest that a capsaicin-rich diet not only offers protection against cognitive decline but also may modify AD-type pathologies in the brain. However, a recent study suggested that higher spicy food intake was associated with worse memory decline in an open cohort study in China.[16] However, cognitive status was assessed in that study with subjectively self-reported memory loss, and participants with higher spicy food consumption in this study were less educated. Whether a capsaicin-rich diet is protective against AD in humans needs further investigation in the future.

**Table 1: Characteristics of AD patients and CNs.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>AD (n = 55)</th>
<th>CN (n = 55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>67.8 ± 8.1</td>
<td>65.5 ± 7.0</td>
<td>0.106</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>30 (54.5)</td>
<td>28 (50.9)</td>
<td>0.849</td>
</tr>
<tr>
<td>Education (years), median (IQR)</td>
<td>6.0 (6.0–9.0)</td>
<td>12.0 (9.0–12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE, median (IQR)</td>
<td>14.0 (5.5–18.5)</td>
<td>28.0 (27.0–29.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFQ, median (IQR)</td>
<td>4.0 (4.0–8.0)</td>
<td>8.0 (4.5–10.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AD: Alzheimer disease; CN: Cognitively normal control; SD: Standard deviation; IQR: Interquartile range; MMSE: Mini-mental status examination; FFQ: Food frequency questionnaire.

Figure 1: Association between FFQ and MMSE scores. (A) FFQ scores were positively associated with MMSE scores in AD patients and CNs; n = 110. (B) FFQ scores were positively associated with MMSE scores in non-AD participants; n = 131. Partial correlation analysis: *P* < 0.05, two-tailed. AD: Alzheimer disease; CNs: Cognitively normal; FFQ: Food frequency questionnaire; MMSE: Mini-mental status examination.
impairment in several trials. Additionally, capsaicin has been proven to be potentially therapeutic to many diseases, including obesity, hypertension, and atherosclerosis, which also act as contributing risk factors for AD. Taken together, our current and previous findings suggest that a capsaicin-rich diet may protect against AD.


