論文の内容の要旨

論文題目

Association between vascular function oscillometrically measured on an upper-arm and cognitive decline among older adults: A multi-facility cross-sectional and prospective study

（オシロメトリック法による上腕部における血管機能測定結果と認知機能の関連：多施設横断および追跡研究）

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1. Introduction

Cognitive decline is a serious and growing issue in the 21st century, with the number of people worldwide living with dementia expected to reach 115.4 million by 2050. Severe cognitive decline beyond normal ageing is clinically known as dementia. As one of the world's most rapidly ageing countries, Japan is facing a severe challenge with respect to the control of dementia, especially among high-risk people aged 65 and over. Related policies, for the purpose of improving the health care and well-being of older people who have cognitive decline, focus heavily on the early detection of cognitive decline. This is principally because there are currently almost no effective established treatments for cognitive decline, making it especially important to detect and control risk factors for cognitive decline at an earlier stage. In recent years, cardiovascular factors have received an increasing amount of attention in relation to cognitive decline because these factors are modifiable, whereas traditional risk factors are unmodifiable. Research findings have implied that arterial stiffness is associated with cognitive decline, although the underlying mechanism for this association is not fully understood. Vascular function, especially decreased arterial compliance, is a significant component of arterial stiffness. Impaired vascular function may contribute to microcirculation damage through increased pulsatile pressure and flow load. If the hypothesised mechanism between impaired vascular function and cognitive decline via augmented pulsatile pressure caused by central artery stiffness is correct, the pulse wave waveform in an upper extremity should also be associated with cognitive

decline. The arterial velocity pulse index (AVI) is a novel vascular function index that characterises the waveform using feature values in its calculation. This index is easily measured oscillometrically on one side of the upper arm, with the patient in a sitting position. Considering that its measurement is based on the pulse wave waveform and considering the known association of AVI value with cardiovascular risk profiles, it is possible that AVI is an independent predictor of future cognitive decline. However, no previous studies have demonstrated an association between AVI and cognitive function. Thus, the aim of the study was to determine whether impaired vascular function, measured oscillometrically on one side of the upper arm, had a significant impact on later cognitive function and its decline.

2. Methods

I recruited participants among the daily users and residents of three long-term care facilities who were available at the time of the study. The study participants completed questionnaire/interview surveys, cognitive function tests, and vascular function tests from October to December 2015. Medical records were also examined to clarify the participants' disease and medication histories. Of a total of 312 older adult candidates, I excluded 210 people based on the exclusion criteria. The ultimate analytic sample at baseline comprised 102 participants. For the prospective assessment, I conducted a follow-up test of cognitive function in the same population 1.5 years after the baseline examination. In the present study, cognitive function was measured as the Mini-Mental State Examination (MMSE), which is the most widely applied instruments for the non-invasive assessment. The MMSE was administered at baseline and follow-up by trained medical staff in each facility using a standardised protocol. The assessment of vascular function was conducted by using the AVI. With the participant in a sitting position, AVI was measured using cuff oscillometry with a PASESA AVE-1500 (Shisei Datum, Tokyo, Japan) by a trained nurse or physician. At baseline, ordinary least squares (OLS) linear regression modelling was used to examine the association between AVI and MMSE score after adjustment for potential confounders. To consider the observed and unobserved effects of each facility, I also used linear mixed-effects modelling to investigate the association when accounting for the impact of the

clustering structure (facility). For the prospective analysis, I used OLS estimation to assess two different impacts of vascular function on later cognitive function after adjustment for potential confounders: (1) the effect of baseline AVI on MMSE score at 1.5-year follow-up and (2) the effect of AVI on the subsequent decline of MMSE score (changes in MMSE score over the years). Statistical significance was defined as $p < 0.05$.

3. Results

Of the 102 participants at baseline, 74.5% (n = 76) were women, and the mean age was 81.9 years (SD = 7.9). The mean AVI was 27.7, and the mean MMSE score was 21.3. The follow-up cognitive function test was successfully conducted for 71 study participants, where the mean MMSE score was 18.3. At baseline, AVI was significantly correlated with MMSE, with a Pearson's correlation coefficient of -0.255 ($p < 0.001$). In the linear regression results, impaired vascular function was significantly associated with decreased cognitive function (β = -0.148; 95% CI: -0.276 to -0.020), after adjusting for potential confounders. In the linear mixed-effects modelling, the association between AVI and MMSE score was also significant after adjusting for potential confounders. Likewise, in the prospective analyses, baseline AVI was significantly correlated with follow-up MMSE score, with a Pearson's correlation coefficient of -0.283 ($p = 0.017$). The linear regression models demonstrated that impaired vascular function at baseline was significantly associated with decreased cognitive function at follow-up, showing that a 10-unit increase in baseline AVI was associated with a 2.6–2.8-point reduction in MMSE score 1.5 years later. Defining the cut-off for baseline AVI as its mean, the group with higher AVI values appeared to have more substantial reductions in their MMSE scores over the study period, compared with the group with lower AVI values although the linear regression model did not indicate a significant association between baseline AVI and subsequent MMSE change.

4. Discussion

This cross-sectional and prospective study showed that impaired vascular function (operationalised as the AVI value) was associated with decreased baseline/follow-up cognitive function (measured with

the MMSE) among the older adult population in Japan. This association was independent of known risk factors for cognitive decline. Additionally, higher AVI values were associated with rapid reduction in subsequent MMSE scores, although this relationship did not show statistical significance. To our knowledge, this is the first study to describe the association between AVI and MMSE score. Increased aortic stiffness results in the augmentation of pulse pressure. This transmits from the central arteries to the microvasculature of end organs such as the brain via peripheral arteries. Given the nature of pulse wave measurement, the AVI could specifically reflect the central aortic waveforms through capturing the enhanced reflected waves. In fact, the AVI could be an independent, non-invasive predictor of aortic systolic blood pressure and aortic pulse pressure according to a previous study. Therefore, it is plausible that vascular function, measured as the AVI value, is associated with the extent of cerebrovascular damage. Thus, the hypothesis that increased AVI value is associated with impaired cognitive function, which was supported by the results of the present study, is in line with previous work. The main strength of this study lies in its multi-facility design and combination of different statistical approaches in the same population, which reinforce the robustness of the study results by taking into account the variability of facilities. Longitudinal changes in cognitive function were also assessed in the prospective analysis, which can contribute to the discussion on the causal relationship between vascular function and cognitive decline. Regarding the study limitations, there was a possible selection bias because the current study sample was selected from users of three long-term care facilities; therefore, the representativeness of the older adult population is limited. In addition, unmeasured influences such as cardio-metabolic factors may have affected the study results.

5. Conclusion

In conclusion, the present study has shown that impaired vascular function, operationalised as the AVI value, is associated with decreased cognitive function among the older adult population in Japan. These findings may support the clinical importance of the AVI as a new index for cognitive decline among the older adult population, as well as providing strong justification for future intervention studies to clarify whether improving the AVI can prevent later cognitive decline.