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CORRESPONDENCE

Proportional changes in the gut microbiome: a risk factor for cardiovascular disease and dementia?

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A recent study published in this journal suggests that the gut microbiome affects physical function in elderly patients with hypertension [1]. Analysis of the gut microbiome is currently a hot topic in research, because of its potential as a novel risk factor for several life-threatening conditions, including hypertension [1] and cardiovascular disease [2, 3]. For example, terminal restriction fragment length polymorphism (T-RFLP) analysis conducted by Emoto et al. revealed that the incidence of coronary artery disease (CAD) is linked to alterations of the gut microbiome [2]. Recently, we also demonstrated that the gut microbiome is independently and closely associated with the presence of dementia using T-RFLP analysis [4]. Although our analysis used a cross-sectional design and the causal relationship has yet to be clarified, comparisons focusing on similarities and differences in the gut microbiome between the CAD and dementia cohorts may be key to a better understanding of the role of the gut microbiome in these diseases.

Therefore, we carried out a preliminary comparison of the two cohorts with regard to the gut microbiome (Fig. 1). The CAD and dementia cohorts show certain differences in the proportions of male vs. female patients and in average patient age [2, 4]. Analysis of the intestinal microbiota of the CAD and dementia cohorts revealed that enterotype I (*Bacteroides* >30%) was most prevalent amongst the healthy volunteers (mean age: 59 years), followed by the CAD control group (62 years), patients with CAD (61 years), patients without dementia (76 years), and patients with dementia (77 years) (Fig. 1). In contrast, the prevalence of enterotype III (others) showed the reverse order. Thus, the prevalence of enterotype I appears to decrease with advancing age and may be inversely associated with the prevalence of vascular risk factors. In general, dementia patients are older and are more likely to have vascular risk factors, such as hypertension and diabetes mellitus [5]. Additionally, both age [6] and dietary parameters [7] are recognized as robust risk factors for the alteration of the gut microbiome.

This comparison between the two cohorts may be affected by the demographic differences in age and sex ratio and by the differing proportions of risk factors. Furthermore, it is difficult to draw solid conclusions given the varying incidences of enterotypes among the groups within

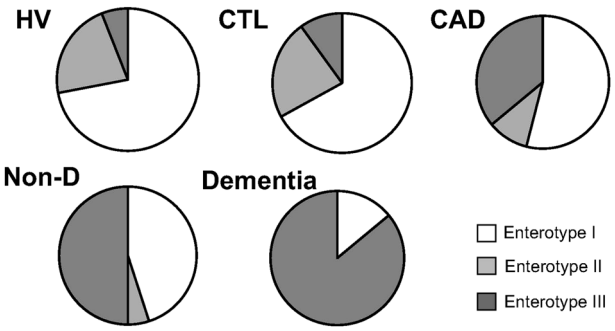

Fig. 1 Enterotype frequencies. Enterotype I (*Bacteroides* >30%) was more likely to be enriched in the younger subjects without vascular risk factors. Healthy volunteers (HV; mean age: 59 years), control group (CTL; 62 years), patients with coronary artery disease (CAD; 61 years), non-dementia patients (Non-D; 76 years), and dementia patients (Dementia; 77 years) belonged to the Kobe **a**–**c** [2] and NCGG **d**, **e** [4] cohorts

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the cohorts. However, analyzing the specific "other bacteria" indicated by enterotype III in more detail may help elucidate the mechanisms underlying the association between the gut microbiome and these life-threatening diseases. We speculate that microvascular inflammation associated with the gut microbiota may cause microvascular dysfunction [8], which could lead to both cardiovascular disease and dementia. Furthermore, the gene-environment-gut microbiome interaction may be associated with a particular disease state [9], and represents an exciting new target for potential disease therapies. Currently, comprehensive dementia research is an important topic in Japan [10]. Assessment of the gut microbiome as a potential risk factor for dementia may result in future healthcare advances. Therefore, further studies that take these factors into consideration are needed to clarify the clinical implications of gut microbiome analysis.

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Compliance with ethical standards

Conflict of interest Research fund: NS, TT (NARO Bio-oriented Technology Research Advancement Institution Project); NS (National Centre for Geriatrics and Gerontology, BMS/Pfizer Japan, Toyoaki Scholarship Foundation, Japan Agency for Medical Research and Development (AMED)).

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