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Vascular lesions in mixed dementia, vascular dementia, and Alzheimer disease with cerebrovascular disease: The Kurihara Project

Kenichi Meguro *, Naofumi Tanaka, Masahiro Nakatsuka, Kei Nakamura, Masayuki Satoh

Department of Geriatric Behavioral Neurology, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, 980-8575, Sendai, Japan

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ABSTRACT

The concept and diagnosis for mixed dementia is not simple, since it is difficult to identify the type and regions of cerebrovascular disease (CVD) responsible for causing dementia. An investigation is needed to confirm the presence of mixed dementia, those who met the criteria for Alzheimer's disease (AD) and those for vascular dementia (VaD). According to the community-based stroke, dementia, and bed-confinement prevention in Kurihara, northern Japan (Kurihara Project), the prevalence of dementia and dementing diseases was surveyed in 2008–2010. Five hundred and ninety people finally agreed to participate (47.0%), and 73 (12.4%) people were diagnosed with dementia according to the DSM-IV. Using MRI, intensive evaluations on CVDs were performed for the 49 dementia patients associated with CVDs (mixed dementia, VaD, and AD with CVD). For the mixed dementia group, all had left subcortical strategic CVDs. These included the caudate head and thalamus. For the VaD group, all patients had at least cortical CVDs or subcortical strategic CVDs. The AD with CVD group had non-strategic CVDs in cortical, subcortical, or other areas in 5 or 6 patients each. Two extreme concepts regarding CVD and dementia are possible. One is that there is no concept for mixed dementia or VaD. An alternative is that the vascular factor should be considered as primary. Our data showed an importance of cortical and subcortical "strategic" areas, the latter included thalamus and caudate head.

1. Introduction

For countries with increasingly large populations of older adults, knowledge of the prevalence of dementia and dementing diseases is necessary for health policy planning. The most common dementing diseases are Alzheimer's disease (AD) and vascular dementia (VaD). The former is a degenerative disease and the latter is a cerebrovascular disease (CVD), thus the strategies on prevention and treatment are different. Six systematic studies on the dementia prevalence have been performed in Japan [1–6]; the data varied from 3.8% to 11.0% in those aged 65+ years, and the AD/VaD ratio varied from 0.7 [2] to 4.1 [6]. We previously reported the prevalence to be 8.5% and 12.4% in those aged 65+ years and 75+ years, respectively, in northern Japan [3,7]. As for dementing diseases, the most common cause was AD with CVD in both populations [3,7].

However, a further investigation is needed to confirm the presence of mixed dementia, those who met the criteria for AD and those for VaD. This status should be different from that which merely accompanies CVDs in AD, i.e., such CVDs in mixed dementia should be located in the "strategic areas," which cause cognitive deterioration even if they are small. Thus the concept and diagnosis for mixed dementia are not simple so far; the biggest reason is the difficulty in identifying the type and regions of CVDs responsible for causing dementia. Confirmation of these etiologically related lesions requires sophisticated neurologic knowledge on the strategic areas [3]. With recent developments of MRI technology, even small signal abnormalities can be easily detected. A non-specialist might easily misdiagnose this condition as mixed dementia or VaD simply because the subject was demented and showed MRI abnormalities.

According to the community-based stroke, dementia, and bed-confinement prevention for the old-old adults aged 75+ years in Kurihara, northern Japan (the Kurihara Project), the prevalence of dementia and dementing diseases was investigated [7]. In the present study, following the previous epidemiologic survey, the CVDs in those with mixed dementia, VaD, and AD with CVD were analyzed. The aim of this study is 1) to examine the relationship between AD, VaD and mixed dementia, and 2) to see the anatomic ("strategic") sites of CVDs that are more related to cognitive impairment.

2. Methods

2.1. Participants

A detailed methodology was described previously [7]. Briefly, according to the Kurihara Project, the prevalence of dementia and dementing diseases was surveyed in 2008–2010. The total population in the city was about 76,708 and the population of the old-old was

* Corresponding author. Tel.: +81 22 717 7359; fax: +81 22 717 7339.
E-mail address: k-meg@umin.ac.jp (K. Meguro).

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about 14,579 (17.9%; November 2010). From among 255 communities in the city, 19 were selected by the officials, and they were asked to participate in the project (target population of 1254). These populations underwent 1) Clinical Dementia Rating (CDR) assessment, 2) neuropsychological tests, 3) blood and urine tests, and 4) MRI scans.

Finally 590 people agreed to participate (47.0%), and 73 (12.4%) people were diagnosed with dementia using the DSM-IV criteria after rating a CDR 1+ status [7]. MRI images of 576 people were successfully analyzed, and an intensive evaluation on CVD was performed for the dementia patients associated with CVDs (n=49, mixed dementia, VaD, and AD with CVD) (see below).

For the blood tests, vitamin B1, B6, and B12, thyroid hormones, HbA1c were determined. The people showed no abnormal findings, nor did by the routine urine tests.

2.2. MRI

MRI examinations were performed using 1.5 T-MRI at the Kurihara Central Hospital, and were used to assess brain atrophy and vascular changes, to allow the diagnosis of the dementing diseases. On MRI images, the signal changes were considered to be CVD, which showed low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and high signal intensity surrounding the low signal intensity areas on FLAIR images. The lesion was operationally regarded as "état criblé" when it was under 4 mm at the maximum size, and as CVD when the size was over 4 mm [8]. Although microinfarcts are considered to have potentially important roles to affect cognitive deterioration [9], we were not able to analyze these in this study because of the limited resolution of routine MRI.

The following areas were defined as "strategic," since even minor CVDs in these regions can cause cognitive dysfunction [10,11]: thalamus, caudate head, anterior limb of the internal capsule, hippocampus, amygdala, basal forebrain, dorsolateral frontal area, and the association cortices of the frontal, temporal, and parietal lobes. The putamen, globus pallidus and deep white matter were defined as "non-strategic" areas, since damage to these areas is not likely to cause cognitive dysfunction. This assessment was made blindly to the diagnosis by neurologists independent of this study on mutual agreement.

2.3. Dementia and dementing diseases

For dementing diseases, "probable" diagnoses (see below) were made by the physician's team, comprised of two neurologists, a psychiatrist, and a physicist. The following diagnosis was performed after a meeting of two neurologists, a psychiatrist, and a physician.

1) AD: People who met the following criteria were considered to have AD, i.e., "pure AD without CVD; the NINCDS-ADRDA criteria for probable AD [12], and no CVD, as shown by MRI.
2) AD with CVD: People who met the following criteria were considered to have AD with CVD: the NINCDS-ADRDA criteria for probable AD, and the presence of CVD as shown by MRI; however, the CVD was considered to be a concomitant lesion, and the CVD areas were not responsible for the cognitive deterioration.
3) VaD: People were considered to have VaD if they met the probable VaD criteria, as per the NINDS-AIREN [13].
4) Mixed dementia: People who met the criteria for AD (NINCDS-ADRDA) [12] AND the criteria for VaD (NINDS-AIREN) [13] were considered to have mixed dementia.

2.4. Ethics

Written informed consent was obtained from all participants and the family. The study was approved by the Ethical Committees of Tohoku University Graduate School of Medicine, Kurihara City, and Kurihara Central Hospital (MRI).

3. Results

Table 1 shows the number (ratio) of people with cortical and subcortical CVDs in each CDR group. Totally 42.9% of the people have CVDs with step by step increase by the CDR severity. The ratio of the people with left subcortical CVDs has a higher tendency in the CDR 1+ group.

Table 2 shows the number of patients with CVDs in the three groups. Overlapping in the cortical, subcortical, and other areas were allowed. Grossly, left subcortical CVDs were noted in dementia patients associated with CVD: for the mixed dementia group, all had left subcortical CVDs. These included "strategic" CVDs such as the caudate head and thalamus. For the VaD group, all patients had at least cortical CVDs or subcortical strategic CVDs. Two patients showed subdural hematoma. The AD with CVD group had non-strategic CVDs in cortical, subcortical, or other areas in 5 or 6 patients each.

Actual distributions of vascular lesions are demonstrated in Table 3. The locations of CVDs were evaluated for the 10 vascular territories, i.e., right or left side of cortical or penetrating branches of anterior, middle, and posterior cerebral arteries. Lesions in other than the mentioned areas (ex. pons, cerebellum, etc.) were not described. Our data showed an importance of cortical and subcortical "strategic" areas, the latter included thalamus and caudate head.

4. Discussion

As shown in the previous report [7], AD with CVD was the most common dementing disease, which coincided with the previous results of 65+ years [3]. The ratio with mixed dementia was greater than the Tajiri Project. As a matter of course, the old-old population was more likely to suffer from CVD than those in the younger population. As earlier described, it is difficult to identify the type and regions of CVD responsible for dementia. Confirmation of this etiologically related CVD requires sophisticated neurologic knowledge. With recent developments of MRI technology, even small signal abnormalities can be easily detected, and thus a non-specialist might easily misdiagnose this condition as VaD or mixed dementia simply because the subject was demented and showed MRI abnormalities.

The results of CVD distributions indicated that bilateral involvement of the basal ganglia region (penetrating branches of middle cerebral artery), or at least unilateral cortical CVD is associated with dementia. For the thalamus, even one CVD at the left side could cause cognitive deterioration to meet the diagnosis of mixed dementia or VaD (referred also to as "thalamic dementia"). Global neural disconnection based on even subcortical vascular lesions might be associated with VaD, such as in AD as a disconnection syndrome [14]. Global cortical glucose utilization was related to cognitive decline [15].

Among the "strategic" areas, the thalamus and associated neural networks have been extensively investigated with regard to memory impairment [16,17]. Previously Levasseur et al. [18] examined 7 patients with bilateral thalamic infarcts, who manifested persistent amnesia and frontal lobe signs. They showed diffuse cortical hypometabolism,

Table 1
Number (ratio) of people with cortical and subcortical CVDs in each CDR group.

	n	Any place	Cortical CVD		Subcortical CVD		Others
			R	L	R	L	
CDR 0	217	74 (34.1%)	21 (9.7%)	19 (8.8%)	37 (17.1%)	37 (17.1%)	7 (3.2%)
CDR 0.5	288	124 (43.1%)	36 (12.5%)	28 (9.7%)	52 (18.1%)	62 (21.5%)	12 (4.2%)
CDR 1+	71	49 (69.0%)	16 (22.5%)	20 (28.2%)	20 (28.2%)	28 (39.4%)	5 (7.0%)
Total	576	247 (42.9%)	73 (12.7%)	67 (11.6%)	109 (18.9%)	127 (22.0%)	24 (4.2%)

CVD = cerebrovascular disease, CDR = clinical dementia rating, R = right, L = left.