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Vascular dementia with left thalamic infarction: Neuropsychological and behavioral implications suggested by involvement of the thalamic nucleus and the remote effect on cerebral cortex. The Osaki–Tajiri project

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ABSTRACT

Vascular dementia (VaD) is a condition whereby decreased cerebral perfusion causes cognitive deterioration. We hypothesized that lesions of the anterior nucleus (AN) including the mammillo-thalamic tract cause a decline in the recollection of past episodes/events, and that the left thalamic infarction can cause frontal dysfunction through the "diaschisis." We investigated 18 VaD cases with only left thalamic infarction. ^{99m}Tc-ECD single photon emission computed tomography (SPECT) was used to assess regional cerebral blood flow (CBF). To test the first hypothesis, the scores on the Cognitive Abilities Screening Instrument (CASI) domain Recent memory or the rating on the Clinical Dementia Rating (CDR) domain Memory were analyzed. To test the second hypothesis, we selected the six regions of interest that correlated with the two measures, i.e., word fluency and/or depressive state, as assessed with the Geriatric Depression Scale (GDS). We found that all patients had amnesia, especially in the AN group, six of the eight patients had scores of 1+ on the CDR Memory scale, and all but one disclosed the CASI domain *Recent memory* impairment. There were significant correlations between the left anterior cingulate CBF and word fluency scores, and between the right rectal gyrus CBF and GDS scores. We suggest that these observations are due to a remote effect of the thalamic lesion.

1. Introduction

Vascular dementia (VaD) is a condition in which decreased cerebral perfusion causes cognitive deterioration that interferes with daily life. Three major subtypes of VaD have been proposed: (1) a large infarction that causes deterioration of at least two cognitive domains and subsequently meets the criteria for VaD; (2) multiple infarctions that cause dementia, including cases referred to as multi-infarct dementia (Hachinski et al., 1974), as well as those with white matter lesions that cause executive dysfunction and memory impairment (referred to as subcortical VaD) (Erkinjuntti et al., 2000); and (3) infarctions in "strategic" areas such as the thalamus or caudate head that cause cognitive dysfunction (Szimai et al., 2002).

Among the "strategic" areas, the thalamus and associated neural networks have been investigated extensively with regard to memory impairment (Aggleton et al., 2011; Carlesimo et al., 2011). There are two major thalamic nuclei: the anterior nucleus (AN) of the thalamus including the mammillo-thalamic tract (MTT), which is supplied mainly by the tuberothalamic artery, linked to the mammillary body and hippocampus, and the mediodorsal nucleus (MD), which is supplied mainly by the paramedian artery, linked to the perirhinal cortex. Lesions of the AN and/or MMT are considered to be marked by a selective decline in the recollection of past episodes/events, whereas MD lesions are not.

Furthermore, VaD patients frequently exhibit "extra-memory" symptoms such as depression. Thus the third type, which we refer to as "strategic VaD," is thought to be a good model for analysis of the neuronal network, since symptoms observed in this condition, such as memory or language dysfunction, cannot be attributed simply to the function of small "strategic" areas, but can be viewed as the expression of dysfunction of cortical/subcortical networks.

Diaschisis, a well-known neuroimaging and pathophysiological finding in which thalamic or basal ganglia infarctions cause hypoperfusion in the ipsilateral or contralateral cerebral cortex, was originally proposed as a basis of functional impairment in remote areas. In early studies, Baron et al. (1986, 1992) investigated the relationship between cortical energy metabolism and neuropsychological impairment linked to unilateral thalamic lesions caused by stroke or thalamotomy. Such impairment was reflected in the depression of synaptic activity in both the

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overlying and contralateral cerebral cortices. In particular, thalamic infarctions could lead to word-finding difficulty, with word finding difficulty, aphasia, or amnesia, which could be due to remote effects on other cortical areas. Functional neuroimaging using single photon emission computed tomography (SPECT) or positron emission tomography (PET) may be appropriate to study these effects.

Previously Levasseur et al. (1992) examined seven consecutive patients with bilateral thalamic infarcts who manifested with persistent amnesia and frontal lobe signs. They exhibited diffuse cortical hypometabolism, suggestive of the areas of cortical diaschisis following thalamic infarction. Regarding the laterality, a left side lesion was considered to be more responsible for cognitive deterioration. Shim et al. (2008) described four patients with acute stroke in the left thalamus who exhibited severe amnesia and decreased word fluency, as well as executive dysfunction. SPECT findings indicated that the amnesia observed in the patients was caused by a combination of the left thalamic nucleus and cortical areas. Stenset et al. (2007) reported a case of a 67-year-old right-handed patient with a left thalamic lesion who had an amnesic syndrome with preserved general intellectual function. PET with fluorodeoxyglucose (FDG) showed decreased uptake showed decreased uptake in the frontal, parietal and temporal lobes of the left hemisphere. These results support the importance of the network influencing the activity in areas of the cortex that are responsible for memory.

Systematic studies of "strategic" VaD with left thalamic infarction, especially those focusing on the remote effect in association with neuropsychological findings, have not been performed comprehensively. We used SPECT to examine consecutive outpatients with "strategic" VaD who exhibited infarction only on the left side, and using SPECT and investigated whether the remote effect was associated with cognitive dysfunction.

We hypothesized that (1) lesions of the AN, including the MMT, would be marked by a selective decline in the recollection of past episodes/events, and that (2) left thalamic infarction could cause cognitive deterioration, especially in frontal lobe function, through "diaschisis." These mechanisms may be used to explain the clinical observations.

2. Methods

2.1. Participants

This was a prospective study of data collected on all patients seen in the clinic at the Osaki–Tajiri SKIP Center. The study investigated 120 consecutive outpatients with dementia. The entry criteria were as follows: (1) right-handed; (2) presence of cerebrovascular disease (CVD) only in the thalamus, as shown by magnetic resonance imaging (MRI) (see below); (3) meeting NINDS-AIREN criteriaf or VaD; (4) Clinical Dementia Rating (CDR) (Hughes et al., 1982; Morris et al., 2001) scores of 0.5 or greater; (5) Mini-Mental State Examination (MMSE) (Folstein et al., 1975) scores ≥ 9 to ensure verbal communication during neuropsychological testing, and (6) MMSE scores below the cutoff scores regarding dementia according to each educational year, i.e., a score below 24 (educational level of 10 years or more), a score below 21 (8 years of education), and a score below 17 (6 years of education). The exclusion criteria were as follows: (1) drug treatment that could affect cerebral metabolism, such as anti-depressants and cholinesterase inhibitors; and (2) systemic conditions that might affect cognitive functions, such as vitamin B_1, B_6, B_{12} deficiency, hypothyroidism, or diabetes mellitus, as shown by blood sampling.

The NINDS-AIREN criteria include the presence of CVD, dementia, and a relationship between the two, supported by a temporal relationship between CVD and onset of dementia within 3 months. All patients developed dementia after CVD within 3 months, from 2 weeks to 3 months after the stroke with an average time of 1.52 months. A total of 44 patients with VaD met all the study entry criteria, of whom 20 had bilateral thalamic infarctions with several lacunar infarctions in the deep white matter, accompanying moderate to severe white matter lesions, 18 had a single CVD only in the left thalamus, and six had a single CVD only in the right thalamus. Therefore, the effect of a left thalamic infarction was assessed in 18 patients. No infarctions were detected in any areas except for the left thalamus.

Table 1
Demographics of 18 VaD patients with left thalamic infarction.

ID	Age/sex	Education (years)	Recent stroke (months ago)	Nucleus	Artery
1	71 F	12	1	AN	Tubelothalamic
2	84 M	12	0.5	AN	Tubelothalamic
3	88 M	8	1.5	AN	Tubelothalamic
4	83 F	8	0.5	AN	Tubelothalamic
5	70 F	8	2.8	AN	Tubelothalamic
6	87 M	8	2	AN	Tubelothalamic
7	83 F	8	1	AN	Tubelothalamic
8	82 F	6	0.8	AN	Tubelothalamic
9	83 F	10	3	MD	Paramedian
10	77 M	12	1	MD	Paramedian
11	76 M	12	2.5	MD	Paramedian
12	82 M	10	3	MD	Paramedian
13	84 F	10	0.5	MD	Paramedian
14	72 M	10	2.5	MD	Paramedian
15	70 M	8	0.5	MD	Paramedian
16	88 M	8	3	MD	Paramedian
17	87 M	8	0.8	MD	Paramedian
18	82 F	8	0.5	MD	Paramedian

ID #1 and #3 cases are reported in the text. VaD, vascular dementia; M, male; F, female; AN, anterior nucleus; MD, mediodorsal nucleus.

The demographics of the 18 patients are shown in Table 1. Eight patients exhibited infarction in the AN including MTT, supplied mainly by the tuberothalamic artery, whereas the remaining 10 had infarction in the MD, supplied mainly by the paramedian artery. The MD lesions were all in the anterior and/or medial portions. Thus, the remote effect of the medial frontal lobe (not dorsolateral) was analyzed (see below).

Written informed consent was obtained from the patients and their families. The study was approved by the ethics review committees of the Osaki-Tajiri SKIP Center and Tohoku University Graduate School of Medicine.

2.2. CDR assessment

For the CDR assessment, a clinical team consisting of medical doctors (board-certified neurologists and a psychiatrist) and public health nurses determined the CDR independent of the neuropsychological assessment in the following manner: (1) Before participants were interviewed by the medical doctors, a research nurse specialist or public health nurses visited their homes to evaluate their daily activities. (2) Family members observed the participants' daily activities, and a research nurse specialist or public health nurse visited frequently to evaluate their daily lives. (3) The participants were interviewed by medical doctors to assess episodic memory, orientation, judgment, etc. (4) Finally, referring to the information provided by the family members, the CDRs for all participants were determined at a joint meeting of the medical doctors and a research nurse specialist or public health nurses. A reliable Japanese version of the CDR scales had previously been established (Meguro, 2004).

The CDR is a dementia staging instrument used to rate cognitive function over five levels of impairment from none to maximal (rated as 0, 0.5, 1, 2, or 3) in each of six domains: Memory (M), Orientation (O), Judgment and Problem Solving (JPS), Community Affairs (CA), Home and Hobbies (HH), and Personal Care (PC). Only impairment caused by cognitive dysfunction is rated. Domain-M scores are based on the subjects' episodic memories; domain-O rates according to their time and place orientation. Domain-JPS examines social judgment abilities; domain-CA and domain-HH assess instrumental activities of daily living that are relevant to the individual. Domain -PC represents basic activities of daily living that are common to almost all individuals. Based on the collateral source and participant interviews, a global CDR score is derived from individual ratings in each domain; CDR 0 indicates healthy, and CDR 0.5, 1, 2, and 3 represent questionable, mild, moderate, and severe dementia, respectively.

2.3. Neuropsychological and behavioral assessments

The assessments were administered by trained neuropsychologists, without knowledge of the diagnosis and SPECT findings. The MMSE was used to assess general cognitive function, a word fluency test was performed to evaluate frontal lobe function, and the Geriatric Depression Scale (GDS) (Sutcliffe, 2000) was used to assess depressive state.

The Cognitive Abilities Screening Instrument (CASI) (Teng et al., 1994), total score of 100 and comprising the following subscores, was also performed: *Remote memory* (10 points): personal semantic memory (place and date of birth of the patient) and general semantic memory (direction of sunset, number of minutes in an hour); *Recent memory* (12 points): immediate and delayed (10 min) recall of