Persistent Working Memory Impairment Associated with Cerebral Infarction in the Anterior Cingulate Cortex: A Case Report and a Literature Review

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Abstract:
A 52-year-old man experienced sudden-onset global amnesia and left limb ataxia. An embolism of the right anterior cerebral artery resulted in anterior cingulate cortex (ACC) infarction, and working memory dysfunction persisted. The ACC, prefrontal cortex, and bilateral superior parietal lobule exhibited decreased activity on single-photon emission computed tomography (SPECT). The ACC handles working memory formation and is essential for the executive function. The areas showing a decreased activity on SPECT were responsible for the working memory, which corresponded to the observed symptoms. This is the first case in which limited ACC infarction resulted in permanent working memory dysfunction, and SPECT revealed the decreasing working memory in the associated region.

Key words: anterior cingulate cortex, cingulate gyrus, cerebral infarction, stroke, single-photon emission computed tomography, working memory

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Introduction
Activity in the anterior cingulate cortex (ACC) and prefrontal cortex (PFC) comprises working memory, which is required for the executive function (1, 2). In addition, activity in the bilateral superior parietal lobule (SPL) is also associated with the ACC function and related to working memory (3, 4-9).

Previous studies in this field have been based on functional magnetic resonance imaging and did not observe the actual functional decline on single-photon emission computed tomography (SPECT), such as in stroke patients. Furthermore, most reports on ACC dysfunction to date have evaluated cases with chronic changes, including compensatory effects. Isolated cerebral infarction of only the ACC is extremely rare, with only two reported cases thus far (10, 11). Both the cases exhibited transient global amnesia. No reports have described the changes on single-photon emission computed tomography (SPECT) due to acute ACC damage.

To our knowledge, we herein report the first case of sudden-onset permanent working memory dysfunction due to limited ACC infarction that resulted in a functional decline in multiple regions, including the PFC and SPL, according to SPECT. This case is extremely important to consider the neural network associated with ACC.

Case Report
A 52-year-old Japanese man developed sudden global amnesia and left limb ataxia. He was right-handed and a heavy drinker. He had untreated hypertension. Before the onset, he had been able to perform jobs involving calculations without any problems. On admission, the ataxia had improved, which was expected to have been present for about half an hour, but the global amnesia persisted. He repeatedly asked questions such as, “Why I am here?” and “What am I doing now?” We explained the current situation to him, but he forgot about it within a few minutes. No personality changes or
The verbal memory score was low (Table). N-isopropyl-p-iodoamphetamine SPECT imaging revealed a decreased uptake of the tracer in the infarcted ACC, ipsilateral PFC, and bilateral SPL. In addition, the right head of the caudate nucleus, globus pallidus, and thalamus also exhibited a decreased uptake (Fig. 2). These areas of decreased activity were not explained by the blood supply region, and the patient had no vascular stenosis that might have resulted in a decreased blood flow. Furthermore, no older stroke lesions were found. This was believed to purely reflect a functional decline. The patient experienced no recurring episodes suggestive of seizure, and electroencephalography was normal. A re-examination six months later showed persistent impairment of the verbal memory (Table).

The presentation of this case has been approved by the review board and is in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patient.

### Table. Result of the Rivermead Behavioral Memory Test.

| Test                                      | during hospitalization | 6 months after onset |
|-------------------------------------------|------------------------|----------------------|
| Total profile score (/24)                 | 16                     | 18                   |
| Total Screening score (/12)               | 6                      | 9                    |
| Subtests raw scores                       |                         |                      |
| 1st and 2nd name (/4)                     | 0                      | 4                    |
| Belonging (/4)                            | 4                      | 3                    |
| Appointment (/2)                          | 2                      | 1                    |
| Picture recognition (/10)                 | 9                      | 6                    |
| Immediate recall of a short story (/25)  | 4                      | 4                    |
| Delayed recall of a short story (/25)     | 4                      | 2                    |
| Face recognition (/5)                     | 5                      | 5                    |
| Immediate recall of a new route (/5)      | 5                      | 5                    |
| Delayed recall of a new route (/5)        | 3                      | 5                    |
| Immediate recall of a message (/3)        | 3                      | 3                    |
| Delayed recall of a message (/3)          | 3                      | 3                    |
| Total orientation (/10)                   | 8                      | 10                   |

 affective disorders were observed.

His only abnormal vital sign was high blood pressure (168/105 mmHg). Diffusion-weighted magnetic resonance imaging at four hours after the onset revealed hyperintensity in the right ACC (Fig. 1), which was characteristic of cerebral infarction. This infarcted area was supplied by the distal branch of the anterior cerebral artery (ACA), which is the same branch that supplies the premotor area and caused limb ataxia; recanalization was expected before admission. No abnormalities were detected, including vitamin B1, B12, folic acid, homocysteine, protein C, S activity, and antiphospholipid antibody. There were no imaging changes suggesting ACA dissociation in its course. During workup to determine the embolus source, a large patent foramen ovale (PFO) was detected. We strongly suspected the involvement of the PFO, and the PFO was closed with a catheter closure device.

Two weeks after the symptom onset, the Rivermead Behavioral Memory Test was performed, and the patient received a total profile score of 16 (cut-off, 17). Specifically, the verbal memory score was low (Table). N-isopropyl-p-123-I-iodoamphetamine SPECT imaging revealed a decreased uptake of the tracer in the infarcted ACC, ipsilateral PFC, and bilateral SPL. In addition, the right head of the caudate nucleus, globus pallidus, and thalamus also exhibited a decreased uptake (Fig. 2). These areas of decreased activity were not explained by the blood supply region, and the patient had no vascular stenosis that might have resulted in a decreased blood flow. Furthermore, no older stroke lesions were found. This was believed to purely reflect a functional decline. The patient experienced no recurring episodes suggestive of seizure, and electroencephalography was normal. A re-examination six months later showed persistent impairment of the verbal memory (Table).

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### Discussion

This is the first case in which limited ACC infarction resulted in permanent working memory dysfunction, and SPECT revealed a decreased working memory in the associated region, PFC, and bilateral SPL. In addition, specific declines were seen with regard to verbal tasks, which is interesting because this is consistent with the fact that the SPL is related to verbal memory. This is an important case for the consideration of the neural network associated with ACC.

The executive function comprises processing, goal setting, developing plans to achieve the goal, and efficiently performing the required actions. Working memory is essential for this function, as it contains information used to achieve a temporal goal and adds operations to the contents depending on the situation. After the goal is achieved, it is erased, and the process is repeated. The Papez circuit is the classical circuit responsible for working memory. The idea is that the loop-shaped conduction pathways of the hippocampus, papillary body, prethalamic nucleus, cingulate gyrus, and hippocampus are responsible for memory formation (12). Although various models have been derived from this circuit,
Baddeley’s multicomponent working memory model is now generally accepted (13).

The infarcted area in our patient was the ACC (Brodman’s area 24). The activities of the ACC and PFC are involved in working memory performance (1, 2). In the evaluation of working memory, the high-performance group demonstrates high functional connectivity between the ACC and PFC, with activation of the ACC and PFC. The ACC functions in attention control, can suppress competing reactions such as interference and obstruction, and can also manipulate information (14-18). Elderly individuals are vulnerable such as interference and obstruction, and can also manipulate information (14-18). Elderly individuals are vulnerable to alterations in the network system between the ACC and PFC; consequently, they cannot use the network efficiently. Since their attention control is reduced, they extend activity outside the ACC and PFC (3). This patient experienced failure in working memory due to an ACC infarction. As a result, his PFC did not function properly, and the SPECT tracer accumulation was decreased. Brain atrophy due to alcohol consumption was generally noticeable. He may have been vulnerable to changes in the network system to the same extent as elderly individuals, with activation outside the ACC and PFC.

SPECT of the patient also showed a low tracer accumulation in the bilateral SPL, and the verbal memory score was low. Research on the parietal cortex function has largely focused on visuospatial and attentional processing (19-21). Recently, functional neuroimaging studies have reliably associated parietal cortex activity with working memory tasks (22-24). In addition, several studies have reported that repetitive transcranial magnetic stimulation (rTMS) to the SPL can affect working memory (25, 26). The SPL is associated with attention systems that support memory storage and the manipulation and rearrangement of information (2-4, 7). Elderly individuals who are unable to activate their ACC exhibit bilateral SPL activity (3, 5, 6). It has also been indicated that bilateral SPL activity is related to verbal memory tasks (8, 9).

While the ACC is associated with the thalamus, caudate, and claustrum (27), the dorsolateral prefrontal cortex (DLPFC) communicates with the caudate nucleus head and connects to the inner segment of the pallidum and finally with the thalamic nuclei. Loops are also formed between the thalamic nuclei and the DLPFC (28). This neurological connection may be reflected in the patient’s SPECT results (Fig. 1). Executive dysfunction can even occur simply as a result of caudate nucleus impairment (29), while pallidal impairment has been reported to include mild memory and language problems with executive dysfunction (30). In Parkinson’s disease, iron deposition in the pallidum is associated with executive dysfunction (31). Higher brain dysfunction involves the association of many sites rather than a single site, and ACC dysfunction would be expected to result in a reduction in the activity of these associations.

It is interesting that the small lateral infarct in the ACC led to such a widespread decline in the brain function. Isolated cerebral infarction of only the ACC is extremely rare, with only two cases reported thus far (10, 11). In both cases, the symptoms immediately improved, and the clinical courses were similar to transient global amnesia (TGA). In TGA, the finding of an area with a hyperintense signal around the hippocampus is common and appears at a high rate of 55.9% (32). The presence of small areas of ACC infarction as seen in our patient should be investigated in patients with TGA.

This case suggests the presence of a brain function associated with the ACC, but the interpretation is limited based on this one case, and more such cases are needed to achieve a better understanding. In addition, the reading span test and listening span test were more appropriate for assessing the verbal working memory than the Rivermead Behavioral Memory Test. However, such tests could be performed, and the evaluation was not sufficient.
The authors state that they have no Conflict of Interest (COI).

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