Branch atheromatous disease has a stronger association with late-onset epileptic seizures than lacunar infarction in Japanese patients

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Abstract

Objective: To evaluate the relationship between late-onset epileptic seizures and non-cortical infarction (namely, lacunar infarction and branch atheromatous disease [BAD]) in Japanese patients.

Methods: We reviewed the medical records and brain magnetic resonance imaging findings of all patients with ischemic stroke admitted to the Departments of Neurology, Neurosurgery, and Stroke Unit at Kurashiki Central Hospital from 1 January 2011 to 31 December 2012. Patients with lacunar infarction and BAD were enrolled; those with cortical and brain stem ischemic lesions were excluded. We analyzed the clinical features of patients who developed late-onset epileptic seizures after cerebral infarction.

Results: Eighty-five patients with lacunar infarction and 99 patients with BAD were enrolled. Four patients with BAD subsequently developed epileptic seizures (2.2% of total patients, 4.0% of patients with BAD), whereas no patients with lacunar infarction developed epileptic seizures. All patients with epileptic seizures had infarction involving the basal ganglia or thalamus. Three of them had multiple cerebral microbleeds, and two had dementia.

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Conclusions: Patients with BAD, but not with lacunar infarction, might have a higher risk of developing epileptic seizures than the general population. Non-cortical infarctions with involvement of the basal ganglia or thalamus may increase the risk of subsequent late-onset epileptic seizures.

Keywords
Epileptic seizures, lacunar infarction, branch atheromatous disease, basal ganglia, thalamus, magnetic resonance imaging

Introduction
A history of stroke is strongly associated with the risk of epilepsy. Evaluation and management of epilepsy is important for post-stroke patients because epilepsy is an independent predictor of a poor functional outcome. Well-known characteristics of cerebral infarction that influence the risk of seizures include cortical involvement, a larger infarction size, hemorrhagic transformation, and vascular risk factors such as cerebral microbleeds (CMBs) and hypertension. Although less frequently, subcortical infarction has been postulated to have a relationship with epileptic seizures.

Subcortical small deep brain infarctions are common in Japan. The pathogenesis of subcortical infarcts varies according to size: lacunar infarcts of <15 mm in diameter may be related to lipohyalinosis of the small arteries, while infarcts of >15 mm may be caused by branch atheromatous disease (BAD) associated with a parent artery atheroma at the orifice of penetrating arteries. Previous studies have shown that no patients with lacunar infarcts but that 3.5% of patients with other types of subcortical infarcts subsequently developed epileptic seizures. The thalamus and thalamocortical system participate in the generation of generalized seizures and probably in propagation of focal seizures. The basal ganglia also participate in seizure propagation and can modulate thalamic activity. Several case reports suggest that abnormalities of deep brain structures may play a critical role in epileptogenesis.

In the present study, we investigated whether subcortical cerebral infarctions (i.e., lacunar infarcts or BAD individually) can increase the prevalence of epileptic seizures in Japanese patients. We also evaluated whether risk factors for seizures and involvement of the basal ganglia or thalamus could be related to seizures. Part of this manuscript was presented in the 2014 Annual Meeting of the American Epilepsy Society, Seattle. We conducted the present study to provide useful information for clinical practice and to serve as a basis for planning larger cohort studies to establish risk factors for post-stroke epilepsy.

Patients and methods

Patients
Among all patients admitted to the Departments of Neurology, Stroke Unit, or Neurosurgery at Kurashiki Central Hospital, a tertiary care hospital in Okayama, Japan, from 1 January 2011 to 31 December 2012, 1140 patients had a history of or presented with cerebral infarction. By checking the patients’ medical records and brain imaging findings
(magnetic resonance imaging [MRI] and computed tomography) we excluded patients with cortical or brain stem infarctions. Eighty-five patients with lacunar infarctions and 99 patients with BAD of the cerebrum were enrolled. Patients with both types of subcortical infarctions were included in the BAD group. We analyzed the clinical characteristics of patients who developed late-onset post-stroke epileptic seizures, including their known risk factors for seizures such as CMBs, hypertension, dementia, and alcohol consumption and precipitating factors such as sleep deprivation and tiredness. Late-onset seizures were defined as those occurring >2 weeks following the stroke. On the basis of the retrospective and noninvasive study design with assured anonymity, the current study was exempt from the need for local ethics committee approval and informed consent.

**Brain imaging-based classification**

Lacunar infarction was defined as a small (0.2–15 mm in diameter) non-cortical infarction, and BAD was defined as a large (>15 mm in diameter) non-cortical deep brain infarction. To the greatest extent possible, we excluded patients with cortical infarctions according to their medical history and MRI findings. Patients with significant major artery stenosis (>50%) or with embolic infarction were also excluded. Involvement of subcortical nuclei was defined as involvement of the basal ganglia or the thalamus; this was determined with reference to fluid attenuation inversion recovery or diffusion-weighted MRI because T1-weighted images were not available for all patients. CMBs were defined as areas of low intensity in the cerebrum on T2*-weighted MRI (≤5 mm in diameter). Imaging studies were initially analyzed by one reviewer (K.O.), but when it was difficult to determine whether lesions involved the basal ganglia, another reviewer (M.K.) who was blinded to the clinical information checked the images.

**Statistics**

The one-tailed Fisher’s exact test was used in the analysis of contingency tables. The significance level was set at p = 0.05.

**Results**

None of the 85 patients had lacunar infarctions, and 4 of the 99 patients (4.0%) with BAD had late-onset epileptic seizures after cerebral infarction. The characteristics of the patients with seizures are summarized in Table 1, Table 2, and Figure 1. All four patients had BAD that involved the basal ganglia and/or the thalamus in the territory of the lenticulostriate artery. Patients with BAD had a stronger tendency to develop epileptic seizures than those with lacunar infarction, although the difference was not statistically significant. Three patients had CMBs on brain MRI. Patient 4 also showed focally increased signals in the hippocampus and insula on diffusion-weighted

| Table 1. Prevalence of epileptic seizures after small subcortical infarctions. |
|------------------|------------------|------------------|------------------|------------------|
| Features | All patients | Lacunar infarctions | BAD | p value* |
|------------------|------------------|------------------|------------------|------------------|
| Total | 4/184 (2.2) | 0/85 (0.0) | 4/99 (4.0) | 0.081 |
| with BG | 4/147 (2.7) | 0/59 (0.0) | 4/88 (4.5) | 0.125 |
| with CMBs | 3/76 (3.9) | 0/41 (0.0) | 3/35 (8.6) | 0.093 |

Data are presented as n/N (%). *Lacunar infarctions vs. BAD, Fisher’s exact test, one-tailed. BAD, branch atheromatous disease, including coexistent lacunar infarctions; BG, involvement of basal ganglia or thalamus; CMBs, cerebral microbleeds.
Table 2. Demographics of patients with epileptic seizures after small subcortical infarctions.

|                      | Patient 1                      | Patient 2                      | Patient 3                      | Patient 4                      |
|----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| **Sex**              | Male                          | Male                          | Female                        | Male                          |
| **Age at CI onset (y)** | Unknown                      | 53                            | 95                            | 77                            |
| **Age at seizure onset (y)** | 77                          | 54                            | 98                            | 83                            |
| **Seizure type (ILAE, 2010)** | Generalized tonic-clonic seizure/partial seizures evolving to secondary generalized seizures | Left face focal seizures without loss of awareness | Generalized tonic-clonic seizure/partial seizures evolving to secondary generalized seizures | Non-convulsive status epilepticus without coma |
| **Number of seizures** | Once                         | Daily                         | Once                          | On one occasion               |
| **Antiepileptic treatment prescribed** | None                         | Clonazepam, diazepam         | Valproate                     | Zonisamide                    |
| **EEG**              | No epileptiform discharges    | Sharp waves in the right central region | Not done                      | Not done                      |
| **Cerebral infarction** | BAD (n = 1), Lacunar (n = 1) | BAD (n = 1), Lacunar (n = 1) | BAD (n = 2)                   | BAD (n = 1)                   |
| **Involvement of subcortical nuclei** | (+)                          | (+)                           | (+)                           | (+)                           |
| **Cerebral microbleeds** | (-)                          | Subcortex                     | Subcortex, Th, Th             | Th                            |
| **Possible precipitating factors** | Sleep deprivation            | Sleep deprivation, tiredness  | Unknown                       | Unknown                       |

CI, cerebral infarction; EEG, electroencephalography; BAD, branch atheromatous disease; Th, thalamus; P, parietal lobe.
MRI consistent with non-convulsive status epilepticus. Interictal electroencephalography of Patient 2 showed sharp waves in the right central region.

Patients 2, 3, and 4 had hypertension. Patients 1 and 3 had a comorbidity of dementia that could not be further differentiated. Patient 1 had a history of heavy alcohol consumption. Patient 2 had borderline diabetes mellitus.

**Discussion**

In this study, we evaluated the relationship between non-cortical cerebral infarctions and epileptic seizures in Japanese patients. To the best of our knowledge, this is the first study to demonstrate that BAD has a stronger association with late-onset epileptic seizures than lacunar infarction. The prevalence of epileptic seizures in patients with non-cortical infarctions and BAD was 2.2% and 4.0% respectively, suggesting that non-cortical infarctions can be a risk factor for epileptic seizures compared with the prevalence of epilepsy in the general population (0.89%).

Large infarctions involving the cerebral cortex can be an independent predictive factor of late seizures. The results of the current study suggest that, similar to cortical infarctions, the size of non-cortical cerebral infarctions is an important factor leading to epileptic seizures. Moreover,
all patients with late-onset seizures in this study had BAD with involvement of the basal ganglia and/or thalamus in the territory of the lenticulostriate artery. This finding is consistent with a previous study that showed among patients with various subcortical non-lacunar infarcts, only patients with striatocapsular infarcts developed epileptic seizures (3.5% of all patients, 6.3% of patients with striatocapsular infarcts).\textsuperscript{10} Analysis of the clinical manifestations of subcortical infarction (pure motor hemiparesis, pure sensory, sensorimotor syndrome, ataxic-hemiparesis, dysarthria-clumsy hand, and atypical lacunar syndromes) would reveal the role of functional networks in epileptogenesis.

Arboix et al.\textsuperscript{20} reported that hypertension and diabetes were significantly associated with recurrent lacunar infarction and that cognitive impairment was a frequent finding in patients with multiple lacunar infarction recurrences. Although no patients with lacunar infarction developed epileptic seizures in our study, further research should focus on the prevalence of and predisposing risk factors for epileptic seizures in association with cognitive decline in patients with recurrent lacunar infarction.

A major limitation of this study is the inevitable effects of already-known risk factors for epilepsy in patients of advanced age. Brain MRI in three of four patients with epileptic seizures showed CMBs, which are reported risk factors for late seizures.\textsuperscript{21} Dementia, hypertension, and other confounding factors could have influenced the threshold of epileptic seizures in our patients. However, these nonspecific factors were considered to similarly influence both groups of patients.

In conclusion, among non-cortical cerebral infarctions, BAD has a stronger association with late-onset epileptic seizures than lacunar infarction in Japanese patients. Involvement of the basal ganglia or thalamus in the territory of the lenticulostriate artery could be an important factor. Further investigation including larger numbers of patients is warranted to evaluate the risk factors for late-onset epileptic seizures after stroke.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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