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Progressing small vessel pontine infarction includes different etiologies

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Abstract

Background: The aim of this study was to investigate the clinical features of progressing stroke of pontine infarction as small vessel disease. **Methods**: Enrolled 38 acute pontine infarctions were confirmed by magnetic resonance imaging and magnetic resonance angiography at the first and seventh days. Ten patients (26.3%) presented progression (NIH Stroke Scale ≥2 increase within 72 h). **Results**: Progressing patients showed no relation to the size and the distribution of lesion. Expansion of ischemic lesion showed correlation with basilar artery atherosclerosis. Stable lesion related to delayed worsening. **Conclusion**: These findings suggest that progressing stroke may be caused by not only the worsening of blood flow of ischemic lesion but also delayed neuronal death.

Introduction

Following brain infarction, the worsening of neurological deficits can be caused by various etiologies. Increasing edema and enlargement of infarct lesion may be frequently observed, especially if the lesion is large. The embolic stroke may be at risk of recurrent infarction or hemorrhagic transformation. If there is a critical stenosis in the main artery, fluctuating blood pressure (BP) may cause the fluctuation of neurological deficits. The neurological worsening, that is, progressing stroke, can be observed even in small vessel pontine infarction, although a patient undertakes in-hospital treatments.[1,2] From a pathological view point, the atheromatous plaque in the basilar artery (BA) had reported to occlude a branch artery, which penetrates pontine parenchyma, causing ischemic lesion.[3,4] The enlargement of this plaque might participate in the progressing stroke.[5–7] Therefore, elucidation of the clinical mechanism of progressing stroke is anticipated. In this study, we aimed to reveal the clinical features of progressing pontine infarction (PPI) by investigating the clinical-imaging relationship.

Methods

Patients

All procedures in this study were approved by the ethical committee of Research Institute for Brain and Blood Vessels, Akita. Consecutive acute ischemic stroke patients who admitted to the hospital within 24 h from the onset and had ischemic lesion in pons were retrospectively screened between April 2010 and March 2012 (n = 70). All patients consented with written document. Then, 38 cases were enrolled in this study (cardiogenic embolism and severe atherosclerosis of BA were excluded, because this study was focused on investigating the small vessel disease). All patients had undertaken magnetic resonance imaging (MRI: Sigma 1.5T; GE Medical Systems, Tokyo, Japan) on admission and 1 week later. Transverse diffusion weighted imaging (DWI: repetition time 5800 sec, echo time 76.2 sec) and T2-weighted imaging (T2WI: repetition time 3600 sec, echo time 96 sec) with a slice thickness of 5 mm were acquired and DWI on admission was used for the diagnosis. The ischemic lesions in DWI on admission were drawn with shadowgraph as presented in Figure 1A. According to previous papers[8] and an anatomical text book, pontine lesions were classified into V type (localized on the ventral part of pons) and VD type (extended to the dorsal part of pons). Moreover, the ischemic lesion was vertically classified into upper, middle, and lower pons. The assessment of classification was performed by two independent doctors blinded from clinical data. DWI of the second examination was compared with that of the first image. The increased size of the lesion was regarded as the expansion of the lesion. Intracranial arterial findings were assessed by magnetic

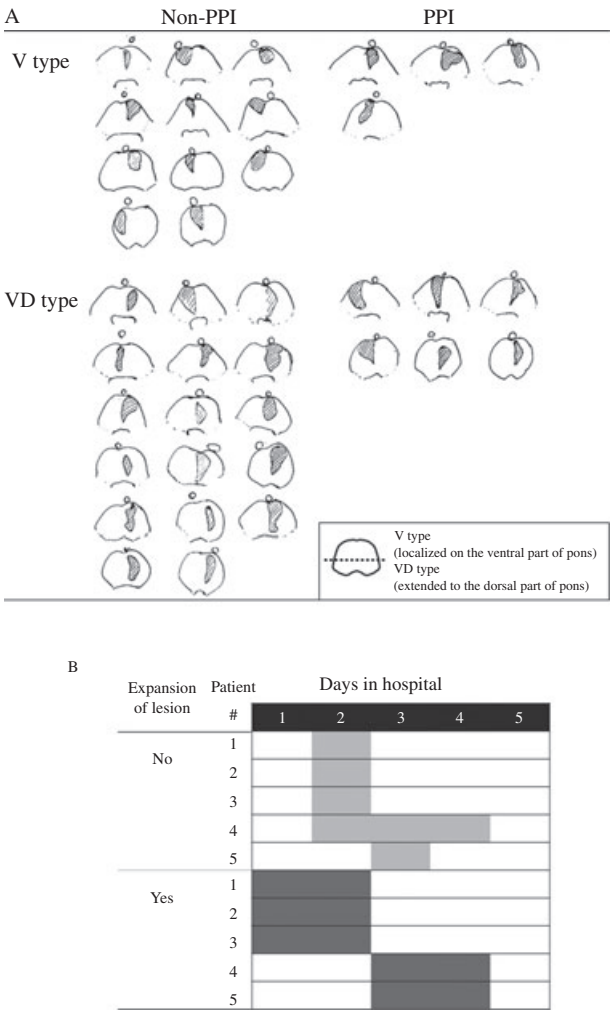

Figure 1. Shadowgraphs of all ischemic lesions (A) and clinical course of PPI patients (B). (A) All cases in both non-progressing and progressing stroke were classified into V type (lesion is located on the ventral part of pons) and VD type (lesion is extended from the ventral to dorsal part of pons). (B) Dates of neurological worsening were observed in progressing stroke patients. Patients were classified based on whether the ischemic lesion was enlarged or not within 1 week. Four of five patients, whose ischemic lesion had not expanded, suffered from the neurological deterioration on the second day in hospital. Three of five patients, whose ischemic lesion had enlarged, suffered from the neurological deterioration on the first day in hospital.

resonance angiography (MRA), which was obtained at the same time as MRI. MRA images were constructed by the three-dimensional time-of-flight method and rendered using the maximum intensity projection method. Tortuosity of BA was assessed by using T2WI and MRA images. At first, at the slice level of ischemic lesion in T2WI, BA on the center of pons and BA shifted to the ipsilateral or contralateral side of the ischemic lesion were classified into the midline, ipsilateral or contralateral groups, respectively. Next, the form of BA was evaluated. If BA was observed in vertically straight or meandering in the coronal view of MRA, they were classified into the straight or meandering, respectively. Moreover, the severity of atherosclerosis in BA assessed by MRA findings was classified into none (no stenosis), mild, and moderate stenosis (less than 50% stenosis). Blood data were sampled at admission prior to the medication started. Vascular risk factors and clinical features of all patients were collected from clinical records. The risk factors were defined as: hypertension (>140 mmHg systolic or >90 mmHg diastolic, or currently prescribed anti-hypertensive drugs), diabetes mellitus (DM: spontaneous blood sugar level >200 mg/dL or currently prescribed anti-diabetic medication), dyslipidemia (>140 mg/dL serum low-density lipoprotein or >150 mg/dL triglyceride, or currently prescribed anti-hyperlipidemia medication), drinking (>180 mL of sake per day) and smoking. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR), using the Japanese Society of Nephrology formula.[9] Neurological severity was assessed by National Institute of Health Stroke Scale (NIHSS) on admission and at 1 month. Progressing stroke was defined as the worsening of NIHSS more than two points within 72 h. Medication was the combination of sodium ozagrel 80 mg DIV ×2/day, edaravone 30 mg DIV ×2/day and cilostazol 100 mg PO BID following the guideline.[10]

Statistical analysis

Data were presented as number with percentage or as mean ± standard deviation (SD). The prevalence of risk factors was compared using Pearson's χ^2 test. Comparison of mean value was performed using Kruskal–Wallis one-way analysis of variance (ANOVA). Logistic regression analysis was performed on the tortuosity and atherosclerotic severity of BA, and odds ratio (OR), and 95% confidence interval (CI) were calculated. All statistical analyses were performed with JMP9 (SAS Institute, Cary, NC).

Results

PPI was observed in 10 patients (26.3%). All of these patients suffered from the worsening of motor paresis. Additionally, three patients showed the worsening of dysarthria. Clinical features of all patients are presented in Table 1. PPI patients showed severer neurological deficits indicated by NIHSS at 1 month compared with non-PPI ($P = 0.05$: 5.9 and 3.6, respectively). Other factors including BP, blood data, and clinical risk factors did not show any significant difference between non-PPI and PPI groups. As shown in Table 2, we assessed the relation

Table 1. Clinical features of all patients.

	Total	Non-PPI	PPI	*P*-value
n	38	28	10	ns
% of female	47.4	42.9	60.0	ns
Age (mean ± SD)	75.2 ± 8.1	75.4 ± 8.0	74.6 ± 8.8	ns
Hypertension (%)	78.9	78.6	80.0	ns
DM (%)	34.2	35.7	30.0	ns
Dyslipidemia (%)	34.2	28.6	50.0	ns
Drinking (%)	15.8	14.3	20.0	ns
Smoking (%)	39.5	39.3	40.0	ns
NIHSS				
On admission	5.1 ± 4.0	5.0 ± 4.1	5.3 ± 3.7	ns
At 1 month	4.2 ± 5.2	3.6 ± 5.6	5.9 ± 3.7	0.05
Blood sample				
Glucose (mg/dL)	123.8 ± 30.7	122.9 ± 31.9	126.3 ± 28.5	ns
Fibrinogen (mg/dL)	360.7 ± 69.5	370.8 ± 73.4	332.5 ± 50.1	ns
CRP (mg/dL)	0.32 ± 0.40	0.33 ± 0.44	0.29 ± 0.31	ns
TG (mg/dL)	5.1 ± 4.0	5.0 ± 4.1	5.3 ± 3.7	ns
LDL (mg/dL)	118.0 ± 47.5	119.3 ± 51.5	115.3 ± 36.3	ns
eGFR (mL/min per 1.73 m^2)	72.2 ± 26.3	72.8 ± 29.3	70.6 ± 15.9	ns

PPI, progressing pontine infarction; SD, standard deviation; DM, diabetes mellitus; NIHSS, National Institute of Health Stroke Scale; CRP, C-reactive protein; TG, triglyceride; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. *P*-value is calculated by χ^2 test.

Table 2. The relation between admission delay and neurological worsening.

Onset-admission (hour)	Non-PPI	PPI
≤2	3 (10.7)	2 (20)
2–6	2 (7.1)	2 (20)
6–12	5 (17.9)	2 (20)
12≤	18 (64.3)	4 (40)
Total	28	10

The values are given as *n* (%). PPI, progressing pontine infarction.

between the admission delay and the neurological progression. The mode was at the timing of 12 h≤ both in the groups of non-PPI and PPI. The distribution was not different between non-PPI and PPI.

Regarding spatial distribution of the ischemic lesion, no significant difference was observed about the ratio of V and VD types between non-PPI and PPI (Table 3 and Fig. 1A) while non-PPI and PPI tended to exist in middle (50.0%) and lower pons (50.0%), respectively. The expansion of ischemic lesion within 1 week was more frequently observed in PPI compared with non-PPI (50.0% and 28.6%, respectively), although there was no statistical difference ($P = 0.220$).

For exploring the influence of BA lesions on the ischemic focus, the tortuosity and wall irregularity of BA were evaluated (Table 3). BA was mostly shifted to ipsilateral side of the ischemic lesion in non-PPI (57.1%) and was located on the midline of pons in PPI (60.0%). The distribution of BA tortuosity was significantly different ($P = 0.024$), and logistic regression analysis revealed that midline BA was a significant predictor of PPI (OR: 5.5, 95% CI: 1.16–26.02). Moreover, moderate atherosclerotic change in BA was at a significant risk of PPI (OR: 8.3, 95% CI: 1.49–46.70).

As only half of the PPI patients exhibited the expansion of the ischemic lesion, the relation between the expansion of the lesion and the period of neurological worsening was evaluated (Fig. 1B). All of the patients who showed no expansion indicated that the neurological worsening started at the second or third day while three of five patients who showed the expansion of the lesion indicated that the neurological worsening started from the first day following onset. Moreover, four of six patients who had moderate atherosclerosis of BA showed the expansion of the ischemic lesion.

Discussion

In this study, the occurrence of PPI was related to the severity of atherosclerosis of BA and not related to the distribution of the ischemic lesion. Moreover, half of PPI did not show the expansion of the ischemic lesion.

It has been reported that the penetrating arterial infarction sometimes express the neurological worsening.[6,7,11] Especially, pontine infarction tends to progress compared with cerebral deep penetrating artery infarction.[12–15] Regarding the feature of pontine infarction, it can be pointed out that the neurological symptoms are various depending on the distribution of the lesion.[16] Actually,

Table 3. Pathological features of ischemic lesion and basilar artery among non-PPI and PPI patients.

n (%)	Total	Non-PPI	PPI	
Spatial distribution of ischemic lesions				
Horizontal				
V type	15	11 (73.3)	4 (26.7)	$P = 0.968$
VD type	23	17 (73.9)	6 (26.1)	
Vertical				
Upper	5	3 (60.0)	2 (40.0)	$P = 0.511$
Middle	17	14 (82.4)	3 (17.6)	
Lower	16	11 (68.8)	5 (31.2)	
Expansion of lesion	13/38 (34.2)	8/28 (28.6)	5/10 (50.0)	$P = 0.220$
Pathological findings of basilar artery				
Tortuosity				
Midline	12	6	6	OR 5.5 (1.16–26.02)
Shifted	26	22	4	
Contra/Ipsi	8/18	6/16	2/2	
Atherosclerosis				
None-Mild	29	25 (86.2)	4 (13.8)	OR 8.3 (1.49–46.70)
Moderate	9	3 (33.3)	6 (66.7)	

PPI, progressing pontine infarction; V type, the lesion localized on the ventral part of pons; VD type, the lesion extended to the dorsal part of pons; Contra, contralateral; Ipsi, ipsilateral; OR, odd ratio and the parenthesis is 95% confidence interval. *P*-value is calculated by χ^2 test.

the neurological deficits were reported to be different between patients whose lesion was localized in the ventral part of pons and patients whose lesion was extended from ventral to dorsal part of pons.[8] Recent reports mentioned that the ischemic lesion located in the lower pons showed a tendency of progressing stroke compared with the lesion located in the upper and middle pons.[17,18] Meanwhile, our data showed that there was no relation between worsening of symptoms and localization of ischemic lesion both in horizontally and vertically. Although we assessed the expansion of the lesion during 1 week, the actual lesion size was not measured because the lesion was observed only by MRI-DWI, which may reflect cytotoxic edema. Therefore, final lesion size should be investigated by using fluid-attenuated inversion recovery (FLAIR) images, and to be planned as a future study. Moreover, the neurological deterioration was reported to be related to the worsening of penetrating arterial blood circulation in pons.[19] On the contrary, another paper mentioned that BA atherosclerosis did not show the influence on the worsening of pontine infarction.[18] Our data may support the relation of atherosclerotic change in BA to the occurrence of progressing stroke.

Then, we investigated the factors which relate to the enlargement of the ischemic lesion and the atherosclerotic change in BA in patients of PPI. Our results suggested that cases who suffer from neurological worsening at their very early phase had a stronger atherosclerotic change in BA and showed the expansion of the ischemic lesion. Cases who started neurological worsening at the second day or later of the onset showed neither any relation to the atherosclerosis in BA nor the expansion of the ischemic lesion. Therefore, it can be said that the PPI may be caused by two etiologies: (1) the worsening of blood circulation to pontine parenchyma because of the atherosclerotic change in BA and (2) the neuronal damage independent from blood circulation. The second etiology could be explained by the delayed neuronal death in which initial ischemic insult triggered neuronal damage, but it takes a few moments to be clinically distinctive.[20] In the future, we have to explore the evidence of delayed neuronal death in the progressing stroke.

This is a retrospective analysis and all of the patients did not take MRI FLAIR image which could indicate the final infarct lesion. Only some patients took MRI examination immediately after the neurological worsening. So we compared the lesion size in the images of MRI-DWI obtained between on admission and at 1 week which is routinely performed in this hospital. Accordingly, this study was not able to analyze the relation between the neurological worsening and the temporal change in the lesion size. It can be said that transient worsening caused by brain edema was not detected.

The limitation of this study was the number of the cases who showed the progressing stroke. In the future, prospective study should be planned to be able to apply statistical analysis. Nevertheless, we examined each case precisely about the symptoms, clinical course, and MRI findings. Therefore, it can be considered that we obtained enough data to analyze the feature of PPI.

In summary, the clinical features of PPI may be the atherosclerotic plaque in BA causing the worsening of

blood flow into pontine parenchyma and the neuronal damage caused by initial ischemic insult, instead of the specificity of the lesion distribution.

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Authorship

T. N. conducted this study and performed the statistical analysis. M. S. carried out the support of statistical analysis. Y. I. performed the screening of patients' data. A. S. participated in setting up and coordination of this study.

Conflict of Interest

T. N.: speaking fees, AstraZeneca, Boehringer Ingelheim, Novartis, Otsuka, Pfizer; consultancy, Sanofi, Takeda. M. S.: none. Y. I.: none. A. S.: consultancy, Pfizer.

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