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Benzodiazepine receptor imaging with iomazenil SPECT in aphasic patients with cerebral infarction

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To investigate the relationship between prognosis of aphasia and neuronal damage in the cerebral cortex, we evaluated the distribution of central-type benzodiazepine receptor (BZR) binding in post-stroke aphasics with [^{123}I]iomazenil and SPECT. We performed iomazenil SPECT in six aphasic patients (aged from 45 to 75 years; all right-handed) with unilateral left cerebral infarction. Three patients showed signs of Broca's aphasia and the other three Wernicke's aphasia. Cerebral blood flow (CBF) imaging was performed with [^{123}I]iodoamphetamine (IMP). The regions of interest (ROIs) on both images were set in the cerebral cortex, cerebellar cortex and language-relevant area in both hemispheres. Three patients were classified in the mild prognosis group and the other three in the moderate prognosis group. The left language-relevant area was more closely concerned with the difference in aphasic symptoms than the right one in both BZR and CBF distribution, but the ipsilateral to the contralateral ratio (I/C ratio) in the language-relevant areas in the BZR distribution was significantly lower in the moderate prognosis group than in the mild prognosis group, although no difference was seen for these values between the two groups in the CBF distribution. These results suggest that BZR imaging, which makes possible an increase in neuronal cell viability in the cerebral cortex, is useful not only for clarifying the aphasic symptoms but also for evaluating the prognosis of aphasia in patients with cerebral infarction.

Key words: benzodiazepine receptors, cerebral blood flow, single photon emission computed tomography, aphasia, cerebral infarction

INTRODUCTION

IT IS KNOWN that aphasia frequently occurs in patients with infarcts and ruins the social aspects of their life. Recovery from aphasia with stroke is usually remarkable during the first three months and then continues slowly, and their symptoms become fixed by one year after onset.[1–3] The severity of aphasia soon after onset is the most important factor affecting recovery.[3] It is therefore important to grasp the precise pathophysiology early and to estimate the future condition as soon as possible so that patients can undergo language rehabilitation and return to work, but the symptoms of aphasia vary greatly and cannot always be predicted from the morphological features observed by x-ray CT or MRI.[4,5] In contrast, positron emission CT (PET) and single photon emission CT (SPECT) have revealed functional suppression occurring in the morphologically-intact regions and related them to the aphasic symptoms.[4–7]

Recently a SPECT tracer, [^{123}I]iomazenil (ethyl-5,6-dihydro-7-iodo-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]-benzodiazepine-3-carboxylate), was developed for central benzodiazepine receptor (BZR) imaging.[8–12] Central BZR is found exclusively in the membranes of neurons.[13] Histopathological studies indicate that decreased BZR density is associated with a reduction in neuron density.[13,14] Clinical studies indicate that central BZR binding is a sensitive marker of ischemic damage in the brain,[15] and that there is a CT-negative region of neuronal injury in the ipsilateral cortex remote from the subcortical infarction[15] and the subcortical hematoma.[16] Recent reports indicate the usefulness of BZR imaging for major

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Table 1 Clinical features and prognosis of aphasia

Patient no.	Age (years) and Sex	Location of infarct	Phase	Type of aphasia	Severity of aphasia					Prognosis
					at onset	after 1 month	after 3 months	after 1 year	after 2 years	
1	45 F	Cortical [left frontal]	Chronic	Broca	0	3	4	4	4	Mild
2	53 M	Sub-cortical [left corona radiata]	Sub-acute	Broca	1	3	4	5	5	Mild
3	63 M	Cortical [left frontal and temporal]	Chronic	Wernicke	1	2	3	3	3	Moderate
4	70 M	Cortical [left temporal]	Chronic	Wernicke	1	3	4	4	4	Mild
5	75 M	Cortical and sub-cortical [left temporal and striatum]	Chronic	Wernicke	1	2	3	3	3	Moderate
6	61 M	Sub-cortical [left corona radiata and putamen]	Chronic	Broca	0	0	1	2	2	Moderate

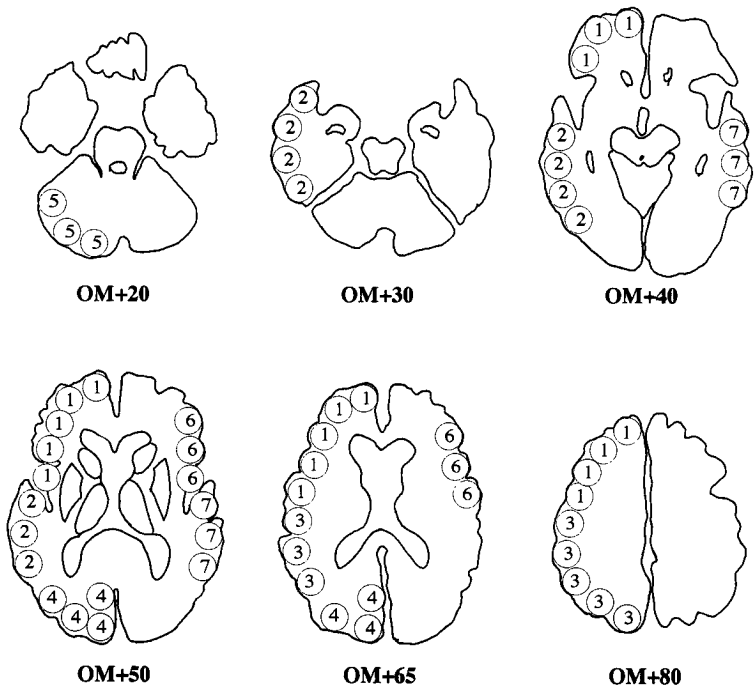

Fig. 1 Regions of Interest (ROIs) on the BZR images were set in the cerebral cortex [frontal (①), temporal (②), parietal (③) and occipital cortex (④)] and cerebellar cortex (⑤) of the affected hemisphere, as well as the mirror regions in the nonaffected hemisphere with 13-mm-diameter circular ROIs in the same regions set on the CBF images. ROIs were also set in both the left and right language-relevant areas [Broca's (⑥) and Wernicke's areas (⑦)] of the cerebral cortex.

cerebral artery occlusive disease[17] and incomplete brain infarction of reperfused cortex,[18] but there have been few detailed reports regarding BZR imaging by means of iomazenil SPECT in patients with disorders of higher cortical function, such as aphasia, due to cerebral infarction.

To investigate the relationship between neuronal damage in the cerebral cortex and the prognosis of aphasia, we used [^{123}I]iomazenil and SPECT to evaluate the distribution of central BZR binding in aphasic patients accompanied with cerebral infarction.

MATERIALS AND METHODS

Patients

Six aphasic patients (five men and one woman) with unilateral left cerebral infarction in the territory of the middle cerebral artery were examined in a Phase III

Fig. 2

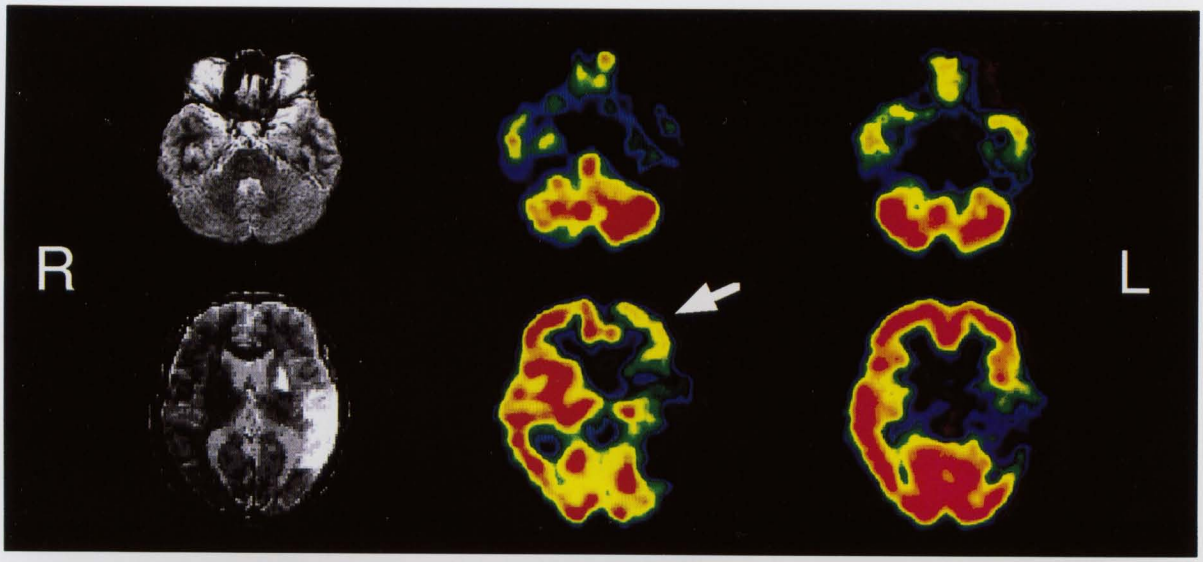

Fig. 3

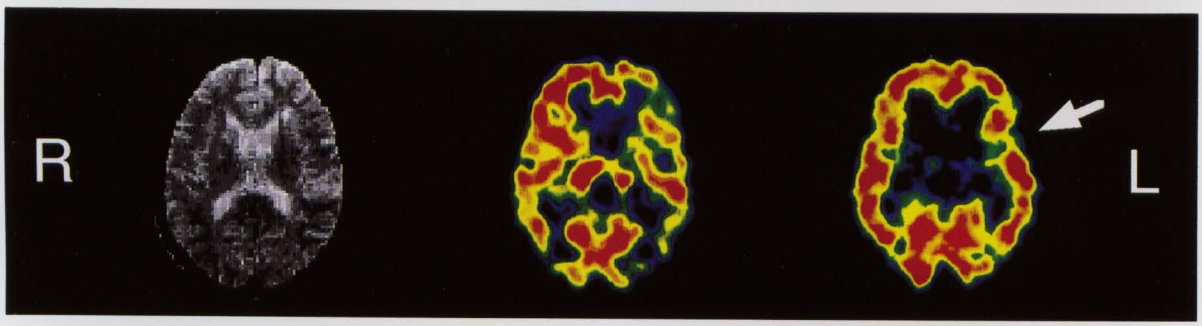

Fig. 2 MRI T_2 (left), CBF (center) and BZR (right) images obtained in the chronic phase in a 75-year-old male (patient 5) that classified the patients with a grade of a moderate prognosis. Although decreased CBF distributions were seen in the right cerebellar cortex due to a remote effect and the left frontal cortex (white arrow) due to a hypoperfusion area around the infarction, these distributions were not seen in the BZR images and the defective area containing Wernicke's area was wide. He had Wernicke's aphasia.
Fig. 3 MRI T_2 (left), CBF (center) and BZR (right) images in the sub-acute phase in a 53-year-old male (patient 2) that classified the patients with a grade of a mild prognosis. Although no infarct was found in the cortical area on MRI, the BZR images showed a slightly defective area in the cortical area containing Broca's area (white arrow). He had Broca's aphasia.

clinical trial of [^{123}I]iomazenil from October 1, 1994 to March 31, 1995. Table 1 summarizes the clinical data for each patient, such as the location of the infarct, the type of aphasia, and the severity of aphasia. The age of these patients ranged from 45 to 75 years (mean ± SD, 61.2 ± 11.0). All patients except patient 5 had right hemiparesis at onset. Three patients (patients 1, 2 and 6) had Broca's aphasia (Broca group), whereas the other three patients (patients 3, 4 and 5) had Wernicke's aphasia (Wernicke group). The type of aphasia was determined at 1 month after the stroke onset. The iomazenil study was carried out on day 14 (with day 0 being the day of onset) in patient 2, day 44 in patient 6, day 121 in patient 4, 13 months in patient 5, 16 months in patient 1, and 5 years and 10 months after onset in patient 3. Cerebral blood flow (CBF) imaging with N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) and morphological imaging such as MRI or x-ray CT were also performed in all patients. None of the patients had an infarct in the cerebellum or right cerebral hemisphere on MRI or x-ray CT. None of the patients had taken benzodiazepine derivatives. All patients were right-handed. These studies were approved by the Institutional Review Board of Nippon Medical School Hospital. Written informed consent was obtained from all patients before the start of the study.

Severity of Aphasia

The severity of aphasia was evaluated with the aphasia severity rating scale of the Boston diagnostic aphasia examination[19] at onset, and at 1 month, 3 months, 1 year and 2 years after the stroke onset. This severity rating is a scale of the capacity for oral communication ranging from grade 0 for "no communication possible" to grade 5 for "no perceptible handicap," as follows: grade 0, No communication possible; 1, Communication possible only by examiner's questioning and guessing; 2, Patient carries

Table 2 Comparisons between Broca's and Wernicke's aphasia groups

		Broca group	Wernicke group	Significance
Severity score	at onset	0.3	1.0	n.s.
	1 month after	2.0	2.3	n.s.
	3 months after	3.0	3.3	n.s.
	1 year after	3.7	3.3	n.s.
Left B/W ratio	CBF distribution	0.88 (0.13)	1.34 (0.30)	$p < 0.05$
	BZR distribution	0.83 (0.10)	1.41 (0.32)	$p < 0.05$
Right B/W ratio	CBF distribution	0.96 (0.08)	1.04 (0.04)	n.s.
	BZR distribution	0.91 (0.05)	0.92 (0.04)	n.s.

Values are mean (SD)
B/W ratio = (value in Broca's area/value in Wernicke's area)
$p < 0.05$ using Mann-Whitney U-test between Broca's and Wernicke's aphasia groups

Table 3 Comparisons between mild and moderate prognosis groups

		Mild group	Moderate group	Significance
Age (years)	at onset	55.4 (13.2)	64.0 (8.8)	n.s.
Duration (years)	from onset to iomazenil study	0.6 (0.7)	2.4 (3.1)	n.s.
Severity score	at onset	0.7	0.7	n.s.
	1 month after	3.0	1.3	$p < 0.05$
	3 months after	4.0	2.3	$p < 0.05$
	1 year after	4.3	2.7	$p < 0.05$
Value in language-relevant area (left) (ml/100 g/min)	CBF	40.8 (7.7)	28.0 (10.0)	n.s.
I/C ratio in language-relevant area	CBF distribution	0.85 (0.06)	0.75 (0.09)	n.s.
	BZR distribution	0.92 (0.05)	0.82 (0.07)	$p < 0.05$

Values are mean (SD)
Value in language-relevant area = [(value in Broca's area + value in Wernicke's area)/2]
$p < 0.05$ using Mann-Whitney U-test between mild and moderate prognosis groups

share of conversation but range of information exchanged is limited; 3, Speech is defective in form and content but patient can convey almost all ideas; 4, Obvious handicap is present although speech is largely correct and there is no limitation on expression; and 5, Residual aphasia with only subjective difficulties.

At 1 year after onset, we classified the patients with a grade of 0 or 1 as a severe prognosis group (severe group), a grade of 2 or 3 as a moderate prognosis group (moderate group), and a grade of 4 or 5 as a mild prognosis group (mild group). Three patients were classified in the mild group and the other three in the moderate group.

SPECT Device

A ring-type single photon emission computed tomograph (HEADTOME SET 080; Shimadzu Co., Ltd.; Kyoto, Japan) was used to measure the distribution of radioactivity in the brain. The scanner simultaneously produces 32 tomographic axial slices. A low-energy high-resolution collimator was used for data acquisition. Data were recorded on a 128 × 128 matrix. A Butterworth and Ramp filter was used for image reconstruction. The planes of both BZR and CBF imaging were set parallel to the orbitomeatal (OM) line. The in-plane and axial spatial resolutions of the scanner were 8.5 mm and 17.5 mm with FWHM (full width at half maximum), respectively.

Evaluation of Central BZR Binding by [^{123}I]Iomazenil

All patients except patient 2 (111 MBq) received 167 MBq of [^{123}I]iomazenil by intravenous bolus injection of 1.5 mL of solution into the right cubital vein. Dosimetry estimates for [^{123}I]iomazenil were within the dose range acceptable for clinical use.[10] Before the study, the patients were given oral potassium iodide to prevent contamination of the thyroid by the administered radioactivity.

SPECT imaging was performed from 7 to 22 minutes (mid-scan time: 15 minutes) and from 172 to 187 minutes (mid-scan time: 180 minutes) after the injection, with a data acquisition time of 15 minutes.

The simulation study suggested that the optimal scan time at which the SPECT image best represented the relative BZR binding was 3.0–3.5 hours post-injection.[11] In the present study, iomazenil images obtained at 180 minutes after injection were used for the analysis of the central BZR distribution.

Evaluation of CBF by [^{123}I]IMP

All patients also underwent a perfusion study. The perfusion study was quantitatively performed with 222 MBq of IMP by intravenous continuous injection into the right cubital vein for 1 minute according to the IMP autoradiographic method.[20,21] The CBF images were obtained with the same scanner and collimator as used in the iomazenil study.

The interval between the iomazenil SPECT and IMP SPECT studies was 5 to 7 days in all patients except patient 1 (about 2 months). No changes in the neurological symptoms were noted in any of the patients during this interval.

Regions of Interest

Regions of Interest (ROIs) on the BZR images were set in the cerebral cortex and cerebellar cortex of the affected hemisphere, as well as the mirror regions in the nonaffected hemisphere with 13-mm-diameter circular ROIs in the same regions set on the CBF images. ROIs were also set in both the left and right language-relevant areas (Broca's and Wernicke's areas) of the cerebral cortex. Figure 1 shows ROIs set in the cerebral cortex and cerebellar cortex.

The value in the language-relevant area was calculated in both hemispheres as follows: [(value in Broca's area + value in Wernicke's area)/2]. The data analyses of these regions were performed for the ipsilateral to the contralateral ratio (I/C ratio).

The value in Broca's area to value in Wernicke's area ratio (B/W ratio) was calculated in both hemispheres as follows: (value in Broca's area/value in Wernicke's area).

Statistical Analysis

The statistical significance of differences between two groups was examined by the paired Wilcoxon U-test and Mann-Whitney U-test.

RESULTS

Presentation of Images in Two Patients

Figure 2 shows the MRI, CBF and BZR images obtained in the chronic phase in patient 5 with Wernicke's aphasia. Although decreased CBF distributions were seen in the right cerebellar cortex and the left frontal cortex, these distributions were not seen in the BZR images.

Figure 3 shows the MRI, CBF and BZR images in the sub-acute phase in patient 2 with Broca's aphasia. Although no infarct was found in the cortical area on MRI, the BZR images showed a slightly defective area in the cortical area containing Broca's area.

Comparison of Broca and Wernicke Groups

Table 2 shows comparisons of the Broca and Wernicke groups in relation to the severity score, left and right B/W ratio in the CBF and BZR distributions. No significant difference was seen in the severity score or right B/W ratio in either the CBF or BZR distribution of the two groups, but significant differences were seen in the left B/W ratio in both the CBF and BZR distributions (CBF: $p < 0.05$; BZR: $p < 0.05$), and the grade of difference in the left B/W ratio of the two groups was stronger in the BZR distribution (1.41/0.83 = 1.70) than in the CBF distribution (1.34/0.88 = 1.52).

Comparison of Mild and Moderate Groups

Table 3 shows comparisons between the mild and moderate prognosis groups in relation to the age at onset, duration from onset to the iomazenil study, the severity score, and values in the language-relevant areas in both the CBF and BZR distributions. No significant difference was seen between the two groups in relation to age, duration or the severity score at onset, but significant differences were seen in the severity score at 1 month, 3 months and 1 year after onset ($p < 0.05$). And the I/C ratio in the language-relevant areas in the BZR distribution was significantly lower in the moderate group than in the mild group ($p < 0.05$), although no difference between the two groups was seen for either quantitative CBF or the I/C ratio in the CBF distribution.

DISCUSSION

Evaluation of Severity of Aphasia

We evaluated the severity of aphasia with the severity rating scale of the Boston diagnostic aphasia examination.[19] This scale is an excellent method that can mainly evaluate the grade of communication with patients and can be easily performed even in the acute stage. Gradual recovery of aphasia was recognized from 3 months to 1 year after onset in all patients, but no change was seen between 1 year and 2 years after onset. This suggests that the severity score at 1 year after onset is most important for estimating the prognosis of aphasia in aphasic patients, and no difference was seen between the severity scores in the Broca and Wernicke groups, which agrees with the results of Demeurisse and colleagues[1] indicating that there was no difference between the Broca and Wernicke groups in the comparison of the prognosis. These results suggest that the severity rating scale used in this study is useful regardless of the type of aphasia.

Correspondence of Type of Aphasia with both BZR and CBF Distributions

Significant differences were seen between the Broca and Wernicke groups in the left B/W ratio in both the CBF and BZR distributions although no differences were seen in the right B/W ratio. This result suggests that the language-relevant area in the left cerebral cortex is more closely concerned with the difference in aphasic symptoms than the area in the right cerebral cortex.

The correspondence of aphasic symptoms with the

defective area in the left language cortex was also clearer in the BZR images than in the CBF images. The BZR images clarified the relationship between the type of aphasia and the impaired cortical areas better than the CBF images. A low-uptake area suggesting disappearance of neurons in the BZR images was seen in the left language cortex without any infarct on MRI. Although a decreased CBF in the cerebral cortex is important in subcortical infarction,[4] it is difficult to make a differential diagnosis between a decreased CBF area due to a remote effect and that due to neuronal damage in aphasic patients with subcortical infarction. Nevertheless, with iomazenil SPECT, it was thought to be possible to clearly visualize the grade of neuronal damage in the cerebral cortex in these patients. Hatazawa and colleagues[16] reported that the BZR distribution in the cerebral cortex, apart from the hemorrhagic area was low in aphasic patients with subcortical hemorrhage. In such cases, it is important to evaluate the grade of neuronal damage in the cerebral cortex with iomazenil SPECT.

Correspondence of Prognosis of Aphasia with Both BZR and CBF Distributions

The I/C ratio in the language-relevant areas in the BZR distribution were significantly lower in the moderate group than in the mild group, although no difference was seen between the two groups in these values in the CBF distribution. Heiss and colleagues[6] relate that the persisting structure in the left hemisphere played an important role in recovery from aphasia in a brain PET activation study with [^{19}F]fluoro-deoxy glucose (FDG), but the significance of a non-dominant hemisphere in language processing has also been reported in previous studies,[22,23] and the importance of the right non-dominant hemisphere for recovery of aphasia has been reported.[1,24] It is thought that there is a conversation-related compensatory mechanism in the right non-dominant hemisphere for hypofunction in the left hemisphere. The findings in the brain PET activation study with H_2[^{15}O] by Ohyama and colleagues[7] suggest the importance of the undamaged area in the left dominant hemisphere in addition to the importance of the language-relevant area in the right non-dominant hemisphere in recovered aphasic patients. Our studies with iomazenil SPECT suggest that the left dominant language-relevant areas is more important to the prognosis of aphasia.

Sette and colleagues[13] report that there was no change in the low uptake of [^{11}C]flumazenil in the infarct area during the period from 2 to 60 days after creating an infarct in baboons used as an experimental animal in a PET study. Remote effects such as CCD recognized in the CBF images are stronger in the acute stage of apoplexy than in the chronic stage. Although one of our patients was in a sub-acute stage, it was thought that little change was seen in the BZR distribution from the acute to chronic stage. This suggests that iomazenil SPECT in the acute stage makes it possible to accurately estimate the severity of aphasia because the change in the disturbed pattern is smaller in the BZR image than in the CBF image. Poeck and colleagues[25] report that recovery from aphasia was better in patients with aphasia who started language therapy within 4 months after onset than in those who started later than that, and Kabasawa and colleagues[26] report that bifemelane hydrochloride improves the aphasic symptoms due to cerebral infarction.

Our results suggest that examination of BZR distribution with iomazenil SPECT is important for making an appropriate choice of language therapy or pharmacotherapy soon after onset in aphasic patients with cerebral infarction.

CONCLUSION

Although we examined the relationship between the prognosis of aphasia and the BZR distribution reflecting the grade of cortical neuronal damage in this study, it was anticipated that iomazenil SPECT would be an important examination not only for understanding the pathogenesis and making a prognosis of aphasia, but also for appropriately choosing language therapy or pharmacotherapy soon after onset in poststroke aphasic patients. Because the duration of the clinical trial of [^{123}I]iomazenil was too short and the number of drugs was too few to use for many patients, the number of patients in this study was small. Observation of the prognosis of the patients in this study and further examination of a large number of patients should be done in the future.

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