Ictal Hyperperfusion of Cerebellum and Basal Ganglia in Temporal Lobe Epilepsy: SPECT Subtraction with MRI Coregistration

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The ictal hyperperfusion (compared with the interictal state) of the cerebellum and basal ganglia has not been investigated systematically in patients with temporal lobe epilepsy (TLE). Their ictal perfusion patterns were analyzed in relation to temporal and frontal hyperperfusion during TLE seizures using SPECT subtraction. Methods: Thirty-three TLE patients had interictal and ictal SPECT, video-electroencephalographic (EEG) monitoring, and volumetric MRI. SPECT subtraction with MRI coregistration was performed using commercial software. The presence of ictal hyperperfusion was determined in the ipsilateral and contralateral temporal lobe, frontal lobe, cerebellum, and basal ganglia. Results: All patients showed ictal hyperperfusion in the temporal lobe of seizure origin. Vermian cerebellar hyperperfusion (CH) was observed in 26 patients (78.8%) and semilobar CH was found in 25 (75.8%). Compared with the side of the epileptogenic temporal lobe, there were 7 patients with ipsilateral hemispheric CH (28.0%), 15 with contralateral hemispheric CH (60.0%), and 3 with bilateral hemispheric CH (12.0%). CH was observed more frequently in patients with additional frontal hyperperfusion (14/15, 93.3%; 2 ipsilateral to the seizure focus, 10 contralateral, and 2 bilateral) than in patients without frontal hyperperfusion (11/18, 61.1%). Among 18 patients with temporal hyperperfusion without frontal hyperperfusion, 11 patients showed hemispheric CH (5 ipsilateral to seizure focus, 5 contralateral, 1 bilateral). Hyperperfusion in the basal ganglia (BGH) was seen in 11 of the 15 patients with temporal and frontal hyperperfusion (73.3%) and in 11 of the 18 with only temporal hyperperfusion (61.1%). In 17 patients with unilateral BGH (13 ipsilateral to the seizure focus, 4 contralateral), CH contralateral to the BGH was observed in 14 (82.5%), CH ipsilateral to the BGH was found in 2 (11.8%), and CH bilateral to the BGH was found in 1 (5.9%). Conclusion: During TLE seizures, hemispheric CH occurred not only in contralateral but also in ipsilateral or bilateral cerebellar hemispheres to the side of seizure origin. Although temporal lobe origin seizures associated with additional frontal hyperperfusion produced more frequent hemispheric CH, seizures showing only temporal hyperperfusion without frontal hyperperfusion could produce BGH and CH. To determine the side of hemispheric CH, the most important factor appears to be the side of BGH, not the side of seizure origin.

Key Words: cerebellar hyperperfusion; basal ganglia hyperperfusion; temporal lobe epilepsy; SPECT subtraction

Ictal SPECT has been widely used for seizure localization in patients with intractable partial epilepsy (1,2). In ictal SPECT of epilepsy patients, hyperperfusion is frequently found in the cerebellar hemisphere and basal ganglia as well as in the seizure focus (3–5) and is thought to have a lateralizing value of seizure focus. Cerebellar hyperperfusion (CH) contralateral to the supratentorial epileptogenic area is frequently revealed on ictal SPECT of epilepsy patients (5–7). Harvey et al. (6) suggested that CH is associated with the frontal motor region. Ueno et al. (8) showed that during an electrical seizure, a marked increase in regional cerebral blood flow (CBF) occurred in the epileptic focus, ipsilateral basal ganglia, and contralateral cerebellar hemisphere. Hyperperfusion in the basal ganglia (BGH) is also a common finding on ictal SPECT of temporal lobe epilepsy (TLE) patients with dystonic posturing (9,10), and hyperperfusion in the basal ganglia has been noted on PET of TLE patients with dystonic posturing (11). Thus, it is suggested that the basal ganglia are involved in the generation of ictal dystonic posturing.

Although there are reports of CH to the supratentorial hyperperfusion area on ictal SPECT (2,6,7,9,11), to our knowledge, the relationship of CH and BGH to temporal and frontal hyperperfusion has not been reported. Previous studies of CH using conventional ictal SPECT revealed several problems, including lower spatial resolution, lack of detailed anatomic information, less sensitivity, and inaccuracy (3,5–7).

To investigate the ictal perfusion patterns of the cerebellum and basal ganglia during seizures of TLE, we performed SPECT subtraction with MRI coregistration. The objectives of our study were to elucidate the ictal hyperperfusion patterns of the cerebrum and cerebellum during TLE.
seizures and to evaluate the relationships between supratentorial cortical hyperperfusion, CH, BGH, and epileptic focus.

**MATERIALS AND METHODS**

**Patients**

We retrospectively evaluated 33 patients (18 male, 15 female; mean age, 27.51 ± 10.8 y; age range, 5–49 y) who underwent temporal lobectomy for refractory TLE at the Samsung Medical Center between 1996 and 1999. This study included patients who had ictal and interictal SPECT with volumetric MRI. Exclusion criteria were ictal injections during the secondarily generalized seizures or postictal period, SPECT image of poor quality, SPECT image not including total cerebellum, and multiple areas of hyperperfusion in the extratemporal regions.

The patients were divided into 2 groups according to the hyperperfusion patterns of the supratentorial region on subtracted SPECT: group 1 (patients with only temporal hyperperfusion without frontal hyperperfusion [n = 18; 10 men, 8 women]) and group 2 (patients with temporal and frontal hyperperfusion [n = 15; 8 men, 7 women]).

**Clinical Parameters and Presurgical Evaluation**

Clinical characteristics registered for each subject included age at the time of the first seizure, duration of epilepsy, seizure frequency, existence of aura and secondarily generalized seizures, and semiology of seizures. All patients underwent presurgical evaluation that included a complete medical and neurologic history and examination, brain MRI, video-electroencephalographic (EEG) monitoring, neuropsychologic evaluation, and ictal and interictal SPECT. The times of the onset and the end of the seizure, timing of the radioisotope injection, and seizure semiology were determined by reviewing ictal EEG and replaying the videotape.

The epileptogenic focus was localized on the basis of the scalp EEG, intracranial EEG (if it was done), neuroimaging studies, and surgical outcomes. Eighteen patients had right TLE and 15 had left TLE.

**Intercital and Ictal SPECT Studies**

Brain SPECT was performed using a triple-head Triad XLT system (Trionix Research Laboratory, Twinsburg, OH) equipped with low-energy, high-resolution collimators. The system resolution was 9.2 mm full width at half maximum with a Butterworth filter. Between 30 and 60 min after intravenous injection of 925 MBq 99mTc-ethylcysteinate dimer, a scan of 20 min was acquired with each head rotating 120° in 3° steps, creating 120 raw image sets. Raw data were reconstructed by filtered backprojection using a Butterworth filter (cutoff frequency, 0.6 cycle/cm; order, 3) and displayed in a 128 × 128 matrix (pixel size, 3.56 × 3.56 mm with a slice thickness of 3.56 mm). Attenuation correction was performed using Chang's method (attenuation coefficient μ, 0.12/cm) (12).

Intercital SPECT studies were performed on patients who had no documented seizure activity during the previous 24-h period (or longer). For ictal studies, patients received the radiotracer injection during the clinical or EEG seizure activity. The patients were monitored continuously by a long-term video-EEG monitoring system during this phase. As soon as seizures were witnessed or a seizure button alarm sounded, the radiotracer was injected rapidly by a trained EEG technologist or nurse.

**MRI**

MR scanning was performed with a Sigma 1.5-T scanner (General Electric Medical Systems, Milwaukee, WI). Spoiled gradient recalled (SPGR) volumetric MRI was performed using the following parameters: no gap; 1.6-mm thickness; 124 slices; repetition time/echo time (TR/TE), 30/7; flip angle, 45°; number of excitations (NEX), 1; coronal views. The voxel dimension was 0.875 × 0.875 × 1.6 mm.

Fluid attenuated inversion recovery (FLAIR) MRI was performed for oblique coronal views using the following parameters: 1.0-mm gap; 4.0-mm thickness; 32 slices; TR/TE, 10,002/127.5; NEX, 1. FLAIR MRI was also performed for axial views with a 2.0-mm gap and 5.0-mm thickness. The T2 image was obtained with the following parameters: 0.3-mm gap; 3.0-mm thickness; 56 slices; TR/TE, 5,300/99; flip angle, 90°; NEX, 3; oblique coronal views. T2 axial images were also obtained with a 2.0-mm gap and 5.0-mm thickness.

**Image Processing for SPECT Subtraction with MRI Coregistration**

SPECT subtraction was processed on an off-line Ultra 1 Creator workstation (Sun Microsystems, Mountain View, CA) with a commercial software package, Analyze 7.5 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). All biomedical images were transferred from each scanner console to the UNIX workstation by a 4-mm digital audiotape device.

The SPECT subtraction procedure consisted of 5 steps (13,14):

- Ictal–interictal SPECT registration. Before subtracting each voxel between the ictal and interictal SPECT images, the 3-dimensional position of the interictal SPECT was transformed to the ictal SPECT. In all cases, the root-mean-square distance was within 1 voxel. Correct registration is important for improving the sensitivity of the subtraction technique, and inaccurate registration may produce a false perfusion difference.
- Radioisotope uptake level normalization. Different radioisotope uptake levels were normalized because each patient had a different level of radioisotope uptake. The normalization factor was calculated over the whole brain (15).
- Ictal-transformed interictal SPECT subtraction. To obtain the cerebral perfusion difference, ictal SPECT was subtracted by transformed and normalized interictal SPECT. The difference in the radioisotope uptake level was calculated using pixel-by-pixel subtraction.
- Noise erasing. To erase the subtraction noise, the SD of each subtracted SPECT was calculated. Two SDs were adjusted to erase the noise.
- MRI-subtracted SPECT registration. Accurate anatomic localization of the epileptogenic focus is important for successful epilepsy surgery (12,15). For localization of difference images, we coregistered subtracted SPECT with SPGR MRI of the patient’s whole brain. In most cases, the error ranges of SPECT–MRI registration were within 3 voxels (voxel size, 0.86 × 0.86 × 1.6 mm).

**Interpretation of Subtracted SPECT**

Ictal hyperperfusion of subtracted SPECT was considered significant only when the CBF difference in each pixel of the brain SPECT image between ictal and interictal states was >2 SDs. The location of significant ictal hyperperfusion was determined on MRI by SPECT–MRI coregistration. The presence of ictal hyper-
Results

Demographic and Clinical Data

The mean age of the 33 patients in the study at seizure onset was 14.48 ± 8.38 y (range, 9 mo–35 y). The mean duration of epilepsy was 13.42 ± 8.9 y (range, 2–37 y), and the mean frequency of seizures was 8.65 ± 13.12 per month (range, 3–50.0 per month). The mean seizure duration of ictal SPECT was 91.56 ± 36.02 s (range, 28–188 s), and the mean latency of the radioisotope injection after seizure onset was 24.53 ± 9.24 s (range, 12–50 s).

An aura of epigastric discomfort was reported in 25 patients, a psychic aura (e.g., fear, other emotions, déja vu) was reported in 12, and a vestibular aura was reported in 5. An initial period of motionless staring was seen in 26 patients. Other components of complex partial seizure were oral automatism (n = 20), manual automatism (n = 20), hand dystonia (n = 11), and head version (n = 9). Secondarily generalized tonic–clonic seizures occurred in 16 patients.

Conventional Ictal SPECT Interpretation

Ictal SPECT showed areas of increased uptake of radioactivity at the epileptic foci in all patients (right temporal region [n = 15], left temporal region [n = 18]). CH was observed in 18 patients (54.6%): CH contralateral to the epileptic focus in 14 patients (5 right TLE, 9 left TLE) and CH ipsilateral to the epileptic focus in 4 patients (3 right TLE, 1 left TLE).

Intercital SPECT revealed a focal and unilateral temporal hyperperfusion that is concordant with the seizure focus in 17 patients (51.5%). Among them, decreased contralateral cerebellar perfusion of interictal SPECT was observed in 3 patients (16.7%).

Brain MRI showed structural lesions in 28 patients (84.9%). Hippocampal sclerosis was found in 21 patients, focal cortical dysplasia in 5, and tumor in 2.

SPECT Subtraction with MRI Coregistration

All 33 patients showed ictal hyperperfusion in the temporal lobe of seizure origin (right temporal in 15, left temporal in 18). CH (either hemispheric or vermian) was observed in 29 patients (87.8%) (hemispheric CH in 25 patients [75.8%], vermian CH in 26 patients [78.8%]). In hemispheric CH, 7 patients (28.0%) showed CH ipsilateral to the temporal lobe hyperperfusion, 15 (60.0%) had contralateral hemispheric CH, and 3 (12.0%) showed bilateral hemispheric CH (Table 1; Fig. 1).

In group 1 (n = 18) with only temporal lobe hyperperfusion in the supratentorial regions, 13 patients (72.2%) showed vermian CH, and 11 (61.1%) had hemispheric CH (5 CH ipsilateral to the seizure focus, 5 contralateral CH, 1 bilateral CH). There were 3 patients without CH, including 2 patients with only left temporal hyperperfusion and 1 with bitemporal hyperperfusion and left predominance. In group 2 (n = 15) with temporal and frontal hyperperfusion, CH was observed in 14 patients (hemispheric CH in 13 patients [86.7%], hemispheric CH in 14 patients [93.3%]). Compared with the side of the epileptogenic temporal lobe, there were 10 patients with contralateral hemispheric CH, 2 with ipsilateral hemispheric CH, and 2 with bilateral hemispheric CH. In the 2 patients with ipsilateral hemispheric CH, 1 with right hemispheric CH had diffuse hyperperfusion in the right whole temporal lobe and focal hyperperfusion in the right orbitofrontal region and left internal capsule. The other patient with right hemispheric CH had hyperperfusion in the right temporal lobe and basal ganglia, right frontopolar, and dorsolateral frontal regions. One patient without CH had diffuse hyperperfusion in the right temporal lobe and focal hyperperfusion in the right dorsolateral frontal and left lateral temporal areas.

BGH was seen in 22 patients (66.7%) (13 [39.4%] ipsilateral, 4 [12.1%] contralateral, and 5 [15.2%] bilateral basal ganglia to the epileptogenic side) (Fig. 1; Table 2). In group 1, 11 patients had BGH (61.1%) (6 [54.6%] ipsilateral, 3 [27.3%] contralateral, and 2 [18.2%] bilateral basal ganglia to the epileptogenic side). In 3 patients with contralateral BGH, ictal hyperperfusion was observed in bilateral temporal lobes. In group 2, BGH was seen in 11 patients (73.3%) (7 [46.7%] ipsilateral, 1 [6.7%] contralateral, and 3 [20%] bilateral basal ganglia to the epileptogenic side). One patient with contralateral BGH showed ictal hyperperfusion in the ipsilateral whole temporal lobe and the contralateral frontal region.

Of the 17 patients with unilateral BGH regardless of the epileptogenic focus, CH contralateral to the side of the BGH was observed in 14 patients (82.5%), ipsilateral CH was seen in 2 (11.8%), and bilateral CH was observed in 1 (5.9%). In 2 patients with CH ipsilateral to BGH, 1 had hyperperfusion in the left whole temporal lobe and left basal
ganglia; the other showed hyperperfusion in the right whole temporal lobe, right frontopolar and frontocentral regions, right basal ganglia, and left mesial temporal area. Five patients showed bilateral BGH and 4 of them had CH.

**DISCUSSION**

The cerebellum receives a significant input from the cerebral hemispheres by the corticopontocerebellar pathway, which arises in the motor, premotor, parietal, and occipital cortices (16,17). Because the corticopontine projection provides a predominant excitatory input on the contralateral cerebellar granule cell, interruption of the corticopontocerebellar pathway is considered to be the principal mechanism of cerebellar perfusion change from the supratentorial lesions (contralateral cerebellar diaschisis or contralateral hyperperfusion) (4,17). Crossed cerebellar diaschisis, a well-known phenomenon of blood flow reduction in the contralateral cerebellum caused by the supratentorial lesion, is believed to occur primarily in patients with lesions of the frontal area, parietal cortex, and thalamic and basal ganglia (4,6,7,18,19). Although it is well known that large supratentorial lesions induce crossed cerebellar diaschisis, relatively small lesions with mild metabolic depression have also been noted to produce contralateral cerebellar hypometabolism (20).

Contralateral CH, a condition opposite to that of crossed cerebellar diaschisis, can also occur because of contralateral cerebral hyperperfusion or hypermetabolism of the ictal focus in epilepsy patients. This is commonly observed on ictal SPECT (60%–70%) of epilepsy patients (3,5–7,21), reflecting an alteration of blood flow through a neuronal connection during seizures. Most previous studies reported that CH during seizures was seen on the side contralateral to the supratentorial hyperperfusion area as is found with crossed cerebellar diaschisis (3,5,21). Another study reported that supratentorial hyperperfusion may result in hyperperfusion of the ipsilateral cerebellum, although it was less profound than was contralateral CH (7). Several studies have shown that frontal lobes have extensive efferent projections to the contralateral anterior cerebellar hemisphere (16,22–25); contralateral CH and hypermetabolism have been observed more often in patients with frontal lobe epilepsy than in patients with TLE (23). The mesial temporal lobe has sparse, diffuse, and bilateral (with an ipsilateral predominance) projections to the cerebellum (22–25). Theodore et al. (26) suggested a consistent tendency of lower cerebellar metabolism in the hemisphere ipsilateral to the seizure-generating temporal lobe. Marks et al. (7) reported that most CH occurred in the side contralateral to the frontal lobe hyperperfusion. Other studies showed that TLE

**TABLE 2**

<table>
<thead>
<tr>
<th>Patterns of BGH: Results of SPECT Subtraction</th>
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<tbody>
<tr>
<td>BGH</td>
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<tr>
<td>Total (n = 33)</td>
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<tr>
<td>Hyperperfusion</td>
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<tr>
<td>Group 1* (n = 18)</td>
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<tr>
<td>Group 2† (n = 15)</td>
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<tr>
<td>Total (n = 33)</td>
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<tr>
<td>Ipsilateral‡ (n = 18)</td>
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<tr>
<td>Contralateral§ (n = 15)</td>
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<td>Bilateral (n = 20)</td>
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<tr>
<td>No hyperperfusion (n = 11)</td>
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<td>Values in parentheses are percentages.</td>
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*Patients with only temporal lobe hyperperfusion.
†Patients with temporal and frontal hyperperfusion.
‡Ipsilateral to epileptic focus.
§Contralateral to epileptic focus.
seizures associated with contralateral CH always had a seizure spread to the ipsilateral frontal lobe (21,27). Our study indicated that the hemispheric CH during TLE seizures can be observed in cerebellar hemispheres ipsilateral, contralateral, or bilateral to the side of seizure origin, and the contralateral hemispheric CH occurred more often in TLE seizures associated with frontal hyperperfusion. Vermian hyperperfusion was seen frequently in groups 1 and 2 (with not only temporal lobe hyperperfusion alone but also temporal and frontal hyperperfusion) through SPECT subtraction. It may be postulated that cerebellar vermis has greater amounts of nerve connections with the temporal lobe than does the cerebellar hemisphere.

BGH is also a common finding in ictal SPECT of TLE patients with dystonic posturing (9,10). The basal ganglia have many reciprocal connections with frontal and temporal cortices (6,7,9,10,28–30). Among the hippocampal efferents, the precommissural fornix fibers originating from the subicular complex are distributed to the accumbens nucleus, which projects massively to the ventral pallidum and the caudate nucleus. Clinical and anatomic data support the hypothesis that BGH is probably the result of subcortical activation from the cortical focus through corticostriate connections (31–33). Also, anatomic reciprocal projections underlie the orbitofrontal cortex and the striatum (29). Therefore, seizures originating from the frontal and temporal cortices can easily spread to the basal ganglia. Corticopontocerebellar fibers from multiple cortical areas (primarily frontal areas) converged to the compact fibers in subcortical regions and they pass the basal ganglia. Activation of the frontal cortex containing many corticopontocerebellar pathway fibers may induce stimulation of the ipsilateral basal ganglia and the contralateral cerebellum. On the other hand, because of the clustering of corticopontocerebellar fibers in the basal ganglia, activation of the basal ganglia from temporal lobe seizures may stimulate these corticopontocerebellar fibers more effectively than does activation of focal frontal cortical regions. Therefore, the side of BGH and the side of seizure origin may be an important factor for determining the side of hemispheric CH in TLE. In our study, BGH was commonly observed in both groups of temporal lobe hyperperfusion alone and frontotemporal hyperperfusion (61.1% and 73.3%, respectively). When unilateral BGH (either ipsilateral or contralateral to the epileptogenic area) was seen, hemispheric CH occurred commonly in the side contralateral to BGH (82.5%). Frontal hyperperfusion (contralaterally), temporal hyperperfusion (ipsilaterally and contralaterally), and BGH (contralaterally) may participate in determining the side of hemispheric CH.

Ictal SPECT has become widely used for seizure localization in patients with intractable partial epilepsy (1,2). Spencer (1) reported that the diagnostic sensitivity and specificity of interictal SPECT were 66% and 68% for TLE and 60% and 93% for extratemporal lobe epilepsy. The sensitivity and specificity of ictal SPECT were 90% and 77% for TLE and 81% and 93% for extratemporal lobe epilepsy. However, conventional side-by-side visual analysis of ictal and interictal SPECT images has limitations in identification of the epileptic focus, particularly in patients with extratemporal or otherwise nonlocalized intractable partial epilepsy (34). To accurately identify the seizure focus by SPECT studies, the physician must consider the differences between ictal and interictal SPECT images in terms of the doses of injected radioisotope, the speed of tracer uptake and decay, the patient’s head position, the image slice location, and the timing of the ictal injection with respect to electrographic and clinical seizure onset and end (15,34). SPECT subtraction with MRI coregistration (computer-aided subtraction of the coregistered normalized interictal SPECT from the normalized ictal SPECT, followed by coregistration of the image difference to the MR image) is a method that can improve the sensitivity and specificity of ictal SPECT in localizing the seizure focus (34–36). Because SPECT subtraction with MRI coregistration has a higher spatial resolution and provides more detailed structural information than does conventional ictal SPECT alone, SPECT subtraction with MRI coregistration is able to localize a focal brain region with a significant perfusion difference during the seizures (15,34,36). Recent studies suggest that the sensitivity and specificity of SPECT subtraction with MRI coregistration may surpass those of MRI, PET, scalp-recorded EEG, interictal SPECT, and visual analysis of ictal SPECT (13,15,37).

Previous studies for the diaschisis have used brain SPECT and PET (5,6,19,21,26,27). SPECT or PET studies have their intrinsic problems in localizing focal CBF or changes in metabolism. CBF and glucose metabolism vary over large cortical regions in individual patients. The brain areas with a significant change in CBF or glucose metabolism from normal or the interictal state are difficult to localize accurately because of intersubject and intertest variation and the low spatial resolution of SPECT and PET (38). Furthermore, detailed anatomic information is not available from brain SPECT or PET images alone.

**CONCLUSION**

CH and BGH during seizures of TLE can be contralateral, ipsilateral, or bilateral to the seizure focus. The presence of additional frontal hyperperfusion or BGH was associated more frequently with hemispheric CH contralateral to their sides. However, temporal lobe hyperperfusion appears to be related to ipsilateral and contralateral hemispheric CH.

SPECT subtraction was able to display objectively and accurately the regional CBF differences of the whole brain between the ictal period and the interictal state. Furthermore, SPECT–MRI coregistration can reveal the anatomic location of brain regions with significant CBF changes during seizures.
ACKNOWLEDGMENT

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