Study on neural activity of thalamic sensory nucleus and microstimulation effect in patients with central post–stroke pain

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Abstract

Objective. Using data obtained during thalamic surgery, we considered the essential factors involved in the development of central post–stroke pain (CPSP).

Subjects and Methods. Subjects consisted of 10 cases of CPSP due to unilateral thalamic cerebrovascular disease lesion, and one case with a brain tumor. Their ages ranged from 55 to 70 years old. Stereotactic Vim–Vcpc thalamotomy was performed in 6 cases, thalamic Vim–Vcpc stimulation in 4 cases, and a thalamic biopsy in one case using depth microrecording. Prior to the operation, we studied somatosensory evoked potentials (SEP) to contralateral median nerve stimulation in 7 out of 10 cases with CPSP. Electrophysiological data obtained during surgery consisted of background neural activity (BNA), sensory response (SR) and burst discharge (burst), and responses to microstimulation in the thalamic sensory nucleus.

Results. SEPs (N13, N20) were flat or markedly decreased in all examined cases. From the electrophysiological study during surgery, we could classify patients into 3 groups. In group A (3 cases), we rarely encountered bursts and found SR frequently in the wide area of the thalamic sensory nucleus. In group B (6 cases), we encountered bursts frequently, which were recognized around decreased or voided areas of thalamic neural activity. In 2 of these cases, we found SR in the limited area of the thalamic sensory nucleus (group B–1), however, we could not find SR in this nucleus in the other 4 cases (group B–2). In 2 cases, which were classified into group C, we found a decrease of BNA, few bursts and no SR in the sensory thalamus. We found response to microstimulation in all groups. The perceptive field to microstimulation was not compatible with the receptive field to peripheral natural stimulation. Pain control was achieved in both group A and B.

Conclusions. In cases with CPSP, we found both dysfunction of the lemniscal system and functional change of the spino–thalamo–cortical system. It has been suggested that these functional changes affect perception or conduction of sensory impulses in the lateral sensory thalamus, resulting in the development of CPSP.

Key words: Central post–stroke pain; Thalamus; SEP; Neural activity; Microstimulation
INTRODUCTION

As Dejerine and Roussy made clear in their precise clinicopathological study 4), central post–stroke pain (CPSP) can be ascribed to a thalamic vascular lesion mainly on the ventro–postero–lateral thalamic area. Various studies suggesting the important roles of the thalamus in the genesis of CPSP have been carried out 1,2,3). Though many hypotheses concerning the factors which cause this intractable pain have been proposed 19), the real mechanism of CPSP remains problematic and systematic studies have been lacking. We examined the pathophysiological mechanism of CPSP using CT scan, MRI, PET scan and depth microrecording. These studies revealed that widespread dysfunction of the thalamocortical system occurred in cases of this intractable pain. Electrophysiological and PET studies showed that increased neuronal activities occurred on the relay nuclei around the cerebrovascular disease (CVD) lesion in the sensory thalamus 6,7,9). Hyperactive response to peripheral natural stimulation might occur on the same area, which has been attributed to functional changes associated with reorganization 14,15,22). The thalamic CVD lesion also caused functional change on the cerebral cortex adjacent to the central sulcus 5,6,7,9), resulting in a change of sensory perception. Recently, neuromodulation therapy has been applied for intractable functional disorders of the brain or spinal cord 21). We carried out epidural spinal cord, thalamic, internal capsule (posterior limb), or precentral cortical stimulation 20) for the treatment of CPSP 8,10,11) based on the preoperative or intraoperative neurophysiological data and a hypothesis in the genesis of CPSP.

In this paper, we studied the somatosensory evoked potentials (SEP) before surgery and thalamic sensory neuronal activity and response to microstimulation during surgery in patients with CPSP. Based on these data, we further considered which factors are critical in the development of CPSP.

SUBJECTS AND METHODS

Subjects consisted of 10 cases with CPSP and one case with a brain tumor and their ages ranged from 55 to 70 years old. There were 8 males and 3 females. All these cases complained of continuous intractable pain on the hemibody; 6 cases on the left side and 5 on the right. Pain was caused by unilateral thalamic CVD lesion in 9 stroke cases, spinal cord lesion (cavernous angiom a) in one stroke case and by thalamic tumor (lymphoma) in one brain tumor case. Though various kinds of medical treatments or analgesic injection treatment had been performed, they had been ineffective. In these patients, stereotactic Vim (Ventralis intermedius)–Vpc (Ventralis caudalis parvocellularis) thalamotomy was performed in 6 cases, thalamic Vim–Vpc stimulation in 4 cases, and thalamic biopsy in one case with the aid of depth microrecording 17,18).

Before the operation, we studied SEP in 7 out of 10 cases with CPSP. This was carried out during unilateral median nerve stimulation on the contralateral side. We measured the amplitude and latency of evoked potentials, mainly originating on the thalamus (N13) and sensory cortical area (N20), which were obtained after adding and averaging 200 electrical stimulations on the contralateral median nerve. The stimulating condition was determined
by reference to a flexion of the thumb on the ipsilateral side to electrical stimulation (amplitude 5.0 – 10.0 volt, width 0.2 milliseconds, frequency 2 Hz).

Stereotactic surgery was performed under local anesthesia. After fixation of a stereotactic frame on the patient’s head with pins, we performed an MRI study for target calculation. During the operation, we studied background neural activity (BNA), sensory response (SR) and burst discharge (burst), or response to microstimulation (amplitude 0.1 – 1.0 mA, width 1 milliseconds, frequency 60 Hz, duration 1 second) in the thalamic sensory nucleus. During microstimulation on the sensory thalamus, we examined sensory response or change of pain. Referring to the recording data, we made a therapeutic lesion by electrocoagulation using a high–frequency sine wave current generator in 6 cases. In 4 cases, we implanted a therapeutic electrode on the thalamus, subsequently connected with the IPG installed on the anterior chest. We stimulated the thalamus continuously under optimum stimulating conditions. For the brain tumor case, we inserted a biopsy needle to the thalamic target and absorbed a few pieces of tumor tissue.

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Abbreviation: Vim: nucleus ventralis intermedius, Vcpc: nucleus ventralis caudalis parvocellularis

### RESULTS

SEP study showed that both N13 and N20 were flat during contralateral median nerve stimulation in 4 out of 7 cases with CPSP. In the other 3 cases, the amplitude of N13 and N20 decreased to lower than half compared to those of SEP during ipsilateral median nerve stimulation. Latency delayed over 2 msec in one case and was almost the same in 2 other cases. We achieved good pain control in 3 cases, moderate in 2 cases and fair in 2 cases. There is no definite relationship between the SEP findings and operative results.

In 6 thalamotomy cases, followed from one year to 6 years and 8 months, good pain control was achieved in 3 cases, moderate in one case and fair in two cases (Table 1). These cases were classified into 3 groups. Electrophysiologically, thalamic BNA was relatively preserved in 4 out of 6 cases (group A and B). In group A (3 cases), we rarely encountered bursts and found SR frequently in the wide area of the thalamic sensory nucleus. Microstimulation on the thalamus evoked paresthesia on the corre-
sponding body part, but somatotopic distribution of the perceptive field was narrower than that of the receptive field to peripheral natural stimulation (Fig.1). In group B (1 case), we encountered frequent bursts, which were recognized around decreased or voided areas of thalamic neural activity. We found SR in the limited area of the thalamic sensory nucleus. Microstimulation on the thalamus also evoked paresthesia on the corresponding body part (Fig.3).

In 4 cases treated by thalamic stimulation, followed from one month to 2 years and 2 months, good pain control was achieved in 2 cases, and moderate in two cases (Table 2). In one biopsy case, followed only one week, pain disappeared after insertion of a biopsy needle and suction removal of pieces of tumor tissue for sampling. Electrophysiological study showed thalamic BNA rather increasing than being preserved in all 5 cases. We encountered frequent bursts, which were recognized around the decreased or voided areas of thalamic neural activity (group B). In one of these cases, we found SR in

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**Fig.1** A representative case in group A. This case was a 64 year–old male who complained of intractable pain on the right side due to left thalamic hemorrhage. He was treated by left Vim–Vcpc thalamotomy. This figure represents correlation between receptive field (RF) to peripheral natural stimulation (left figure) with perceptive field (PF) to microstimulation in the thalamus (right figure) shown along the recording electrode. In this case, somatotopographic representation of RF was larger than that of PF. Electrical stimulation in the thalamus during surgery was performed with optimum amplitude as shown in the parenthesis, with one millisecond width, 6 milliseconds interval, and one second duration. A circle along the trajectory shows the point where the sensory response was recognized. The number along the trajectory shows the distance from the tentative target point represented by micron units.

Vim: nucleus ventralis intermedius, Vcpc: nucleus ventralis caudalis parvocellularis
Thalamic neural activity and microstimulation effect in patients with central post–stroke pain

Fig. 2 A representative case in group B.
This case was a 58 year–old male who complained of intractable pain on the right side due to left thalamic hemorrhage. He was treated by left Vim–Vcp thalamotomy. In this case, sensory responses were found on the very restricted area along the trajectory in the thalamus, however, somatotopographic representation of RF was larger than that of PF.

Fig. 3 A representative case in group C.
This case was a 60 year–old male who complained of intractable pain on the left side due to right thalamic hemorrhage. He was treated by right Vim–Vcp thalamotomy. In this case, sensory response was not found along the trajectory but found responses to microstimulation in the thalamus.
the limited area of the thalamic sensory nucleus (group B–1). In this case, studied using two (A and B) electrodes 3 mm apart each during surgery, marked burst discharges with high amplitude and various durations were frequently recognized and SR was rare at the bottom of the thalamus on the anterior A electrode. On the posterior B electrode, neural activity was almost silent at the dorsal to middle part and very low at the bottom part of the thalamus. Only insertion of the therapeutic electrode without stimulation resulted in the cessation of the intractable pain. Though pain recurred a few days later, it was successfully controlled by electrical stimulation thereafter. We could not find SR in the thalamic sensory nucleus in the other 4 cases (group B–2). In one case, marked burst discharges of various durations were frequently recognized on the dorsal part of the sensory thalamus. Insertion of the therapeutic electrode without stimulation resulted in a decrease of the intractable pain. Though pain recurred a few days after, it was controlled by electrical stimulation in an area of marked and high burst discharges with slow oscillation in the sensory thalamus (Fig.4).

**DISCUSSION**

SEP study revealed that the lemniscal system suffered remarkable damage in cases with CPSP. Amplitudes of both N13 and N20 of SEP were flat during contralateral median nerve stimulation in 4 out of 7 examined cases. In an additional 3 cases, they decreased markedly. They were markedly different from cases with localized type CPSP. Our previous study showed that spinal cord stimulation was effective for cases with localized type CPSP, particularly in cases with preserved sensory function or a little SEP change. It was ineffective for those intractable pain cases in which the lemniscal system suffered remarkable damage. It has been suggested that spinal cord stimulation may reduce pain by affecting the function of supraspinal structures, particularly that of the thalamus, through the lemniscal system. Moreover, there was no definite relationship between the SEP findings and operative results. We could not improve functional change in the lemniscal system but were able to affect that in the lateral spinothalamic system by Vim–Vpc thalamotomy or thalamic stimulation.

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**Table 2** Subjects and results of thalamic electrical stimulation treatment for cases with CPSP
Microrecording study on the lateral thalamus during surgery showed the functional changes of the spinothalamic system in patients with CPSP. We classified patients into 3 groups. Group A: The lateral spino–thalamo–cortical pathway was regarded as slightly irritable and showing mild functional change. We rarely encountered bursts and found SR frequently in the wide area of the thalamic sensory nucleus. Group B: The lateral spino–thalamo–cortical pathway was regarded as remarkably irritable and showing moderate to severe functional change. We encountered bursts frequently and found SR or did not in the limited area of the thalamic sensory nucleus. Group C: The lateral spino–thalamo–cortical pathway was regarded as slightly irritable and showing decrease of sensory function. We found decrease of BNA, few bursts, and no SR in the sensory thalamus. The perceptive field to microstimulation in the thalamus was not compatible with the receptive field to peripheral natural stimulation. These findings also suggested functional changes of the sensory thalamus in cases with CPSP. In group A and B, there was a little to moderate difference between findings of peripheral natural stimulation (receptive field) and microstimulation (perceptive field) in the thalamus. In group C, though we could not obtain SR to peripheral natural stimulation,

**Fig. 4** A representative case treated by thalamic Vim–Vcp stimulation.

This case was a 60 year–old female who complained of intractable pain on the left side due to spinal cord hemorrhage (cavernous angioma). She was treated by right Vim–Vcp thalamic stimulation. The right figure shows the original neural activity obtained at each point shown along the trajectory. The number at each neural activity shows a distance from the tentative target point represented by micron units. The left figure shows a stimulating electrode implanted for thalamic stimulation. Electrophysiological study revealed that marked burst discharges with various durations were frequently recognized on the dorsal part of the sensory thalamus. In this case, pain control was achieved with bipolar stimulation mainly on the dorsal part of the sensory thalamus between electrode 3(+) and 2(–), where marked and high amplitude burst discharges with slow oscillation were recognized. Stimulating condition was amplitude 3.5 volts, width 60 microseconds and frequency 40 Hz.
we found sensory effects to microstimulation in the thalamus. Those findings revealed that the sensory thalamic function was not completely destroyed in cases with CPSP.

In cases treated by thalamic stimulation and one case with brain tumor, we encountered an area of marked burst discharges, with occasional high amplitude, in the sensory thalamus. These cases were classified into group B. During surgery, though it was transient, pain was ameliorated or disappeared immediately after implantation of the therapeutic electrode or insertion of a biopsy needle on the irritable thalamus. After starting therapeutic stimulation, pain control was achieved by treating the area of marked burst discharges with slow oscillation in the sensory thalamus, as shown by a representative case. However, we were unable to obtain pain relief in group C, in which we could not find a sensory response or encounter rare burst discharges in the sensory thalamus. This suggests that those marked burst discharges with occasional high amplitude encountered in the sensory thalamus played important roles in the genesis of CPSP.

Previously, our study revealed various kinds of functional changes around the CVD lesion in the sensory thalamus in cases with CPSP. In this study, we could find both dysfunction of the lemniscal system and functional change of the spino–thalamo–cortical system. The latter were recognized as the findings below: changes of receptive fields to peripheral natural stimulation, mismatch of responses to peripheral natural stimulation and to microstimulation, and marked burst discharges with occasional high amplitude encountered in the lateral sensory thalamus. These functional changes might cause abnormal reception or misconduct of the sensory impulses or excitation of the thalamocortical system in the lateral sensory thalamus, resulting in the development of CPSP. Indeed, pain was ameliorated after making a therapeutic lesion on the functionally changed area or by stimulation on the area of marked burst discharges with slow oscillation in the lateral sensory thalamus.

CONCLUSION

In cases with CPSP, we found both dysfunction of lemniscal system and functional change of spino–thalamo–cortical system. It has been suggested that these functional changes affect perception or conduction of sensory impulses in the lateral sensory thalamus, resulting in developing of CPSP.

References

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