平成21年度（第1回）班会議

日　時：　　平成21年5月30日（土曜日）14：00～

場　所：　　東京大学医学部附属病院　新中央診療棟7階大会議室
東京都文京区本郷7－3－1　東京大学医学部附属病院
電話　03-3815-5411

班会議内容：

1．主任研究者より　福島県立医科大学　宇川義一

2．中間評価結果の報告　福島県立医科大学　宇川義一

3．探索的臨床試験の途中経過、および運用上の注意点について
東京大学大学院医学系研究科　大津　洋

4．アンケートの実施について　福島県立医科大学　宇川義一

出席者：宇川義一・望月仁志・榎本　雪・中村耕一郎・村瀬永子・飛松省三・緒方勝也・福留隆泰・清水俊夫・藤巻由実・花島律子・濱田　雅・寺尾安生・大南伸也・松本英之・代田悠一郎・生駒一憲・小森哲夫・阿部達哉・小林正人・齋藤洋一・細見晃一・圓尾知之・杉山憲嗣・田中篤太郎・大橋寿彦・大津　洋・阪本　光・工藤里美

以上29名

平成21年度（第2回）班会議

日　時：　　　平成21年6月27日（土曜日）14：00～

場　所：　　　東京大学医学部管理研究棟2階　第3会議室
東京都文京区本郷7－3－1　東京大学医学部附属病院
電話　03-3815-5411

班会議内容：

1．主任研究者より　福島県立医科大学　　宇川義一

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3．探索的臨床試験の途中経過、および運用上の注意点について
東京大学大学院医学系研究科　大津　洋

4．アンケートの実施について　福島県立医科大学　　宇川義一

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以上17名

平成21年度（第3回）班会議

日　時：　　　平成22年1月11日（月曜日）14：00～

場　所：　　　東京大学医学部管理研究棟2階　第3会議室

東京都文京区本郷7－3－1　東京大学医学部附属病院

電話　03-3815-5411

班会議内容：

1．主任研究者より　福島県立医科大学　　宇川義一

2．探索的臨床試験の途中経過、および運用上の注意点について

東京大学大学院医学系研究科　大津　洋

3．アンケート調査中間報告

東京大学大学院医学系研究科　大津　洋

4．事務連絡その他

出席者：宇川義一・辻　貞俊・魚住武則・玉川　聡・安田千春・梶　龍兒・佐藤健太・宮崎由道・細野裕希・飛松省三・緒方勝也・野村哲司・福留隆泰・清水俊夫・花島律子・濱田　雅・寺尾安生・松本英之・大南伸也・代田悠一郎・生駒一憲・松永　薫・齋藤洋一・細見晃一・圓尾知之・田中篤太郎・大津　洋・工藤里美・高野詩帆

以上29名

VI. 研究成果の発刊に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Yokochi F, et al.	Observation of involuntary movements through clinical effects of surgical treatments	Groenewegen HJ et al.	The basal ganglia IX	Springer	New York	2009	589-595
Saitoh Y, Hosomi K	Capter 2. From localization to surgical implantation.	Ed: Sergio Canavero,	Textbook of Therapeutic cortical stimulation	Nova Science Publishers, Inc	Hauppauge NY	2009	17-32

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hamada M, Ugawa Y, Tsuji S	High-frequency rTMS of supplementary motor area improves bradykinesia in Parkinson disease.	J Neurol Sci	287	143-146	2009
Hamada M, Hanajima R, Terao Y, Terao Y, Okabe S, Nakatani-Enomoto S, Furubayashi T, Matsumoto H, Shirota Y, Ohminami S, Ugawa Y.	Primary motor cortical metaplasticity induced by priming over the supplementary motor area.	J Physiol	587(20)	4845-4862	2009
Hanajima R, Terao Y, Nakatani-Enomoto S, Hamada M, Yugeta A, Matsumoto H, Yamamoto T, Tsuji S, Ugawa Y	Postural tremor in X-linked spinal and bulbar muscular atrophy.	Mov Disord	24(14)	2063-2069	2009
Yugeta A, Terao Y, Fukuda H, Hikosaka O, Okiyama R, Yokochi F, Taniguchi M, Takahashi H, Hamada I, Hanajima R, Ugawa Y	Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson's disease.	Neurology			in press
武智詩子、魚住武則、辻貞俊	反復磁気刺激の治療への応用	臨床神経生理学	37(6)	471-479	2009

Nishio M, Korematsu K, Yoshioka S, Nagai Y, Maruo T, Ushio Y, Kaji R, Goto S.	Long-term suppression of tremor by deep brain stimulation of the ventral intermediate nucleus of the thalamus combined with pallidotomy in hemiparkinsonian patients.	J Clin Neurosci.	16(11)	1489-91	2009
Sako W, Nishio M, Maruo T, Shimazu H, Matsuzaki K, Tamura T, Mure H, Ushio Y, Nagahiro S, Kaji R, Got S.	Subthalamic nucleus deep brain stimulation for camptocormia associated with Parkinson's disease.	Mov Disord	24(7)	1076-1079	2009
Haruo Uguisu, Ryo Urushihara, Yuki Hosono, Kotaro Asanuma, Hideki Shimazu, Nagako Murase, Ryuji Kaji	Very low-frequency rTMS modulates SEPs over the contralateral hemisphere.	J Med Invest			in press
Katsuya Ogata, Tsuyoshi Okamoto, Takao Yamasaki, Hiroshi Shigeto, Shozo Tobimatsu	Pre-movement gating of somatosensory-evoked potentials by self-initiated movements: The effects of ageing and its implication	Clinical Neurophysiology	120	1143-1148	2009
Akihiro Watanabe, Takuya Matsushita, Hikaru Doi, Takashi Matsuoka, Hiroshi Shigeto, Noriko Isobe, Yuji Kawano, Shozo Tobimatsu, Jun-ichi Kira	Multimodality-evoked potential study of anti-aquaporin-4 antibody-positive and -negative multiple sclerosis patients	Journal of the Neurological Sciences	281	34-40	2009

Yasushi Miyagi ,Tsuyoshi Okamoto, Takato Morioka , Shozo Tobimatsu, Yoshitaka Nakanishi, Kazuyuki Aihara , Kimiaki Hashiguchi, Nobuya Murakami, Fumiaki Yoshida, Kazuhiro Samura , Shinji Nagata, Tomio Sasaki	Spectral Analysis of Field Potential Recordings by Deep Brain Stimulation Electrode for Localization of Subthalamic Nucleus in Patients with Parkinson's Disease	Stereotact Funct Neurosurg	87	211-218	2009
横地房子	パーキンソン病とジストニアに対する脳深部刺激療法	Brain & nerve	61	473-483	2009
Shimizu T, et al ,	Electrophysiological assessment of corticorespiratory pathway function in amyotrophic lateral sclerosis	Amyotrophic Lateral Sclerosis			2010年1月号 in press
磯山浩孝, 生駒一憲	パーキンソン病のリハビリテーション	Geriatric Medicine	47(8)	1003-1007	2009
Takeuchi N, Tada T, Toshima M, Matsuo Y, Ikoma K	Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke	J Rehabil Med	41(13)	1049-1054	2009
Sonoo M, Kuwabara S, Shimizu T, Komori T, Hirashima F, Inaba A, Hatanaka Y, Misawa S, Kugio Y	Utility of trapezius EMG for diagnosis of amyotrophic lateral sclerosis.	Muscle and Nerve	39	63-70	2009
Leung A, Saitoh Y	rTMS for suppressing neuropathic pain : a meta-analysis.	The Journal of Pain	10(12)	1205-1216	2009

細見晃一、 齋藤洋一	難治性神経因性疼痛に対する反復経頭蓋磁気刺激療法(rTMS)	機能的脳神経外科	48(1)	4-5	2009

Ⅶ. 班 構 成 員 名 簿

「反復磁気刺激によるパーキンソン病治療の確立研究班」

平成21年度　班員

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事　務　局	宇 川 義 一 高 野 詩 帆	福島県立医科大学医学部神経内科学講座 〒960-1295　福島県福島市光が丘１番地 TEL（024）547-1246 FAX（024）548-3797	教　授

Ⅷ. 業績別刷り

Observation of Involuntary Movements Through Clinical Effects of Surgical Treatments

Fusako Yokochi, Makoto Taniguchi, Toru Terao, Ryoichi Okiyama, and Hiroshi Takahashi

Abstract Involuntary movements are of numerous types. It is difficult to treat involuntary movements by medication, and the mechanisms underlying involuntary movements are unclear. Stereotactic surgery has been effective for the treatment of involuntary movements. Outcomes of surgical treatments are excellent indicators for understanding the clinical differentiation or pathophysiological mechanism of involuntary movements. The clinical observations of involuntary movements following stereotactic surgery are described in this chapter.

1 Introduction

Involuntary movements are of numerous types and it is often difficult to distinguish between the different types of involuntary movements by clinical examination. Furthermore, it can be difficult to treat them by medication. Consequently, involuntary movements have also been treated by stereotactic surgery similarly to parkinsonian tremor. Deep brain stimulation (DBS) has been introduced in stereotactic surgery, and the range of indications in treating involuntary movements has become wider. However, the brain mechanisms underlying involuntary movements are still unclear. The target of stereotactic surgery is in some cases determined from the results of previous experiments and experience. Here, we consider the factors involved in treating involuntary movements by stereotactic surgery based upon our previous experience of its clinical effects.

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2 Methods

2.1 *Subjects*

Twenty-seven patients presenting with involuntary movements, excluding those with Parkinson's disease, were treated by stereotactic surgery. The patients with involuntary movements included 15 with essential tremor, 1 with multiple sclerosis, 6 with hereditary generalized dystonia, 2 with focal dystonia, and 3 suffering from neuroacanthocytosis.

2.2 *Surgery*

Surgery was performed using a Leksell stereotactic frame; tentative targets were determined by MRI, and neural activities were recorded by microrecording during the operation. The operation was performed under general anesthesia for patients with generalized dystonia and neuroacanthocytosis and under local anesthesia for the other patients.

2.3 *Stereotactic Targets*

The targets of stereotactic surgery were determined on the basis of the type of involuntary movement and the body part affected by the involuntary movements. The target for relief of tremor was the thalamus; the target in cases of dyskinesia and choreoballism was the internal pallidum. In patients with dystonia, the body part affected by dystonia should be considered to make an appropriate selection of the target for surgical treatment. The surgical target in the case of generalized dystonia is the internal pallidum, whereas it is the thalamus in the case of focal dystonia of the extremities.

2.4 *EMG Analysis*

Involuntary movements were analyzed using surface EMG carried out before and after surgery. Before the operation surface EMG showed the type and distribution of involuntary movements, whereas after surgery the clinical outcome can be confirmed by the surface EMG recordings.

3 Results

3.1 Tremor

3.1.1 Essential Tremor

Fifteen patients with essential tremor were subjected to stereotactic surgery. In 12 patients with an isolated limb tremor, a unilateral operation of the most affected side, usually the right hand, was performed. The type of surgical procedure in these cases was a thalamotomy in six patients, a pallidotomy in one patient, and nucleus ventralis internedius (Vim) DBS in five patients. In three patients with a combination of limb tremor and cervical tremor, bilateral operations were performed. In two of these patients, bilateral Vim DBS was performed. In the third patient (33 years) with both a limb tremor and cervical tremor, thalamotomy was performed on one side and pallidotomy on the other side, because bilateral thalamotomy can have adverse effects such as dysphonia. Left Vim thalamotomy was performed first, followed by a right pallidotomy. The left thalamotomy diminished the right cervical tremor. Following the right-sided pallidotomy, the left cervical tremor diminished when the patient was in a relaxed position such as when in a supine or relaxed sitting position, but reappeared when the patient straightened his back.

3.1.2 Multiple Sclerosis

Severe postural, action, and intentional tremors were observed in a 34-year-old male patient with multiple sclerosis. Tremor was more prominent in the right limbs than in the left limbs. MRI scanning revealed multiple sclerosis lesions near the right red nucleus. Tremor was observed to be more severe during intended limb action such as holding a glass of water than when only maintaining the posture such as holding the arm, and his condition was diagnosed as Holmes tremor. During surgery, tremor-related neural activities were recorded in the left Vim nucleus. Vim DBS was effective in diminishing the tremor. The alleviation of postural tremor and intentional tremor depends on stimulation intensity. Figure 1 shows the light tracks of his right shoulder, elbow, and wrist during movement in the finger-to-nose test, improving upon DBS.

3.2 Dystonia

3.2.1 Generalized Dystonia

The six patients with primary dystonia include five patients with DYT1 and one with hereditary non-DYT1 dystonia. Abnormal movements associated with generalized dystonia can include other involuntary movements. By definition, postural dystonia

Fig. 1 The images illustrate the light tracks of the right shoulder, elbow, and wrist during movement in the finger-to-nose test in a patient with multiple sclerosis in three conditions. The OFF condition denotes no stimulation. The other two conditions involve stimulation with either 3.5 or 4.6 V with a pulse width of 90 μs and frequency of 160 Hz. Alleviation of postural and intentional tremor depends on the intensity of the stimulation

is observed during posture, and action dystonia is observed during action. The dystonic movement is phasic and observed throughout the body; it is similar to dyskinesia. Other involuntary movements associated with generalized dystonia are tremor or myoclonus. All six patients with generalized dystonia were treated with bilateral pallidal DBS. Spontaneous dystonic movements diminished first, followed later by a reduction of postural dystonia. Finally, action dystonia decreased, although action dystonia of the hand during writing was usually sustained to some extent.

3.2.2 Focal Dystonia

Two patients with focal limb dystonia were treated by unilateral thalamic DBS. One patient with Machado–Joseph disease had painful dystonia of the left upper limb and another patient showed action dystonia of the right upper limb during repetitive movements (task-specific dystonia). In both patients, DBS electrodes were positioned in the nucleus ventralis oralis posterior (Vop) and Vim areas of the thalamus. Bipolar stimulation of the Vop and Vim areas improved focal dystonia in both patients.

3.3 Choreoballistic Involuntary Movements

Three patients with neuroacanthocytosis were treated with bilateral pallidotomy or bilateral pallidal DBS. Before surgery, all patients showed severe involuntary movements including flexion extension of the trunk, ballistic involuntary movements of the extremities, dyskinesias of the tongue, and autophagia. The patients were unable to sit, stand, or eat independently. In two of the patients, bilateral pallidotomies were performed in two separate surgical sessions. In one patient, bilateral pallidal DBS was performed in a single session under general anesthesia. All types of involuntary movement observed in the three patients with neuroacanthocytosis were abolished after the operation (Yokochi and Burbaud 2008).

4 Discussion

Tremors, whether resting, postural, action, or intentional tremors, are known to improve with thalamotomy or Vim DBS (Kumar et al. 2003). However, postural tremor does not improve with pallidotomy. It is recognized in many published studies and from our clinical experience that subthalamic nucleus (STN) DBS improves parkinsonian tremor. There are also some reports showing that STN DBS can lead to an improvement of essential tremor (Plaha et al. 2004). Yokochi et al. (2005) studied the effects of STN DBS on tremor and speculated that it does not directly improve parkinsonian tremor. Parkinsonian tremor does not immediately stop after starting STN DBS, but first shows oscillation of tremor amplitude and then gradually diminishes, sometimes over a few months. Apparently, the effects of Vim DBS and STN DBS on tremor are different, and it is postulated that Vim DBS inhibits the current rising tremor, whereas STN DBS modulates the tremor circuit. Pallidotomy or pallidal DBS can improve parkinsonian tremor under levodopa medication (Yokochi, unpublished observations). In conclusion, the Vim nucleus is a key nucleus in the tremor circuit for connecting the output of the cerebellum to the cortex, and the thalamo-cortical pathway is involved in all modalities of tremor.

In the present study, generalized dystonia showed improvement with pallidal DBS. Each of the various types of involuntary movements associated with generalized dystonia, including spontaneous dystonic movements, postural dystonia, and action dystonia, had a different time course of improvement after starting pallidal DBS. Dystonic movement diminished first, followed by postural dystonia. Finally, action dystonia decreased, although action dystonia of the hand during writing was to some extent sustained. In other words, action dystonia during hand movements is not fully suppressed by pallidal DBS. Figure 2 shows a hypothetical diagram of the connections in the brain related to the three different types of dystonia (from Segawa et al. 2002). The output of the internal pallidum includes ascending and descending pathways. Postural dystonia may be related to the descending pathways from the internal pallidum. Dystonic movements may be related to ascending pathways, such as the pallido-thalamo-cortical pathways, and action dystonia could appear through the thalamo-cortico-spinal pathways. Focal limb dystonia associated with Machado–Joseph disease and task-specific dystonia of the upper limb showed improvement with Vop-Vim DBS. Focal dystonia such as writer's cramp can be improved by the surgical treatment of the Vop-Vim nucleus (Fukaya et al. 2007). The output from the internal pallidum converges in the nucleus ventralis

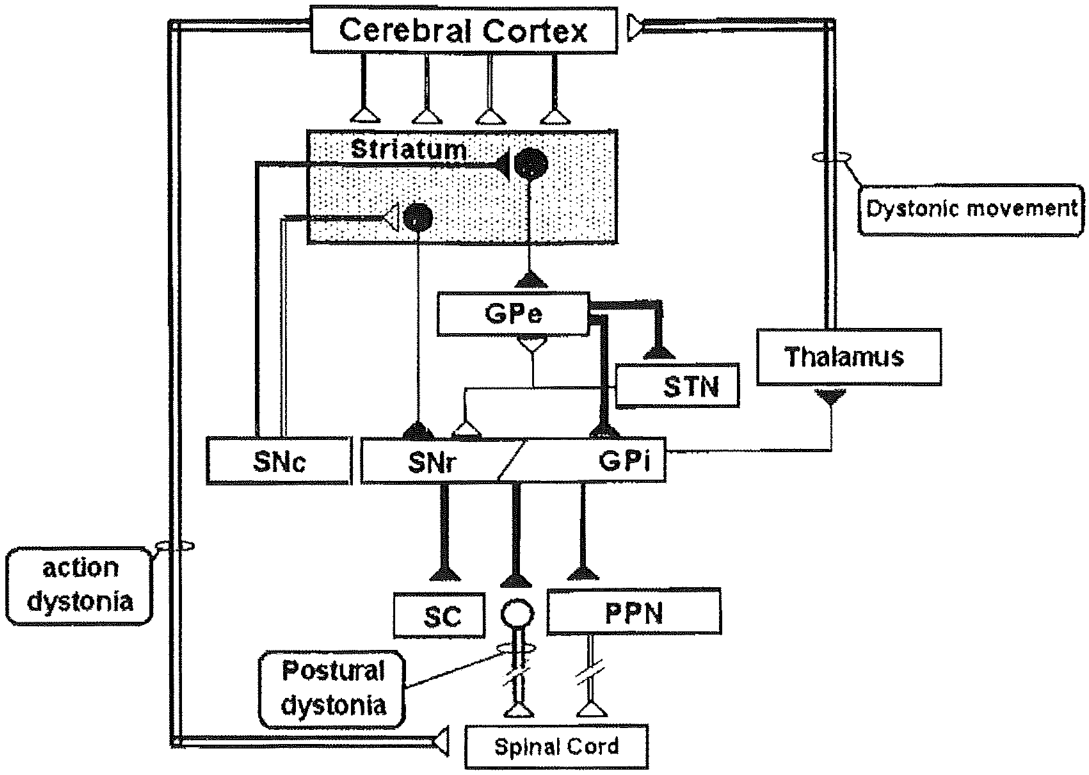

Fig. 2 The schematic was proposed by Segawa and Nomura to explain the mechanism of generalized dystonia observed in DYT 1. Personal communication (2005); modified from Segawa et al. 2002

lateralis (VL), and focal dystonia is assumed to be related to the pallido-thalamo-cortical pathways.

Choreoballistic movements of the face, tongue, trunk, and limbs showed improvement with pallidotomy or pallidal DBS. It has been reported that ballism can be improved by the surgical treatment of either the internal pallidum or the thalamic VL nucleus (Krauss and Mundinger 1996). Choreoballistic involuntary movements are assumed to be related to the pallido-thalamo-cortical pathways.

The type of involuntary movement and the distribution of involuntary movements over the body should be taken into account when selecting a target for stereotactic neurosurgical treatment. The Vim nucleus is a target in the case of tremor of all modalities, including parkinsonian tremor, essential tremor, or cerebellar tremor. The internal pallidum is the target of choice in the surgical treatment of dystonia and choreoballistic movements. However, in the case of dystonia the distribution of involuntary movement over the body is important as well. The two motor systems, namely the lateral motor system and the medial motor system, could be differentially involved in the pathophysiology of dystonia (Kuypers 1982). Dystonia of the extremities may be regulated by the lateral motor system, and the target of choice is the thalamus (VL-Vim nucleus). Dystonia of the face and/or trunk may involve the medial motor system, and the optimal target is the internal pallidum.

5 Conclusions

The factors involved in the choice of the target of stereotactic neurosurgery for involuntary movements are the type of involuntary movement and the body part(s) affected by the involuntary movements. In the case of tremor or choreoballistic movements, the most important factor is the type of involuntary movement, whereas in the case of dystonia, it is a combination of the body part(s) affected by the dystonia and the type of dystonia.

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Yokochi F and Burbaud P (2008) Neurosurgery for neuroacanthocytosis. In: Walker RH (ed) Neuroacanthocytosis syndromes II. Springer, Berlin.

Yokochi F, Okiyama R, Taniguchi M, Takahashi H and Hamada I (2005) Effect of deep brain stimulation on tremor. In: Bolam JP, Ingham CA, Magill PJ (eds) The Basal Ganglia VIII. Springer, Berlin. pp 407–413.

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Chapter 2

FROM LOCALIZATION TO SURGICAL IMPLANTATION

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ABSTRACT

In its landmark paper introducing MI ECS for the treatment of central pain, Tsubokawa et al (1991) included a brief description of the localization of the motor cortex:

"*Location of the motor cortex was estimated by bony landmarks with conventional methods. Paramedian incision was made 1-4 cm lateral to the midline contralateral to the painful area. The trephination was then placed over the estimated area of the motor cortex. ...The locations of the sensory and motor cortices were confirmed from phase reversal of the N20 wave of somatosensory evoked potential recorded from the electrode. When the electrode was moved from the sensory cortex to the motor cortex, the N_{20} wave turned positive. The location of the motor cortex was again confirmed by motor evoked potential recoded in response to stimulation with the electrode. The motor cortex was mapped as carefully as possible and the electrode was placed in the region where muscle twitch of painful area could be observed at the lowest threshold*".

Identification of the precise location of the central sulcus remains one of the key steps in this kind of surgery, and several techniques have been used for this purpose, although they have not been systematically compared. Most neurosurgeons use classical anatomical landmarks to determine the exact position for a craniotomy (chapter 1). Somatosensory evoked potentials (SSEP) and intraoperative motor evoked potential (MEP) measurements are also employed. In recent years, navigation systems have become increasingly important.

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