Table 2
Clinical characteristics of 27 patients.

	Childhood-onset rapidly progressive type (CORP)	Late-onset slowly progressive type (LOSP)
N (M:F)	19 (9:10)	8 (3:5)
Age at epilepsy onset (mean)	2 m~9 y (4 y 4 m)	6 y 6 m ~ 28 y (16 y)
Period between epilepsy onset and development of frequent seizures (mean)	0 d ~ 7 y (1 y 4 m)	6 m ~ 8 y 9 m (3 y 4 m)
Period between epilepsy onset and development of hemiplegia (mean)	2 m~7 y (3 y)	1 y1 m ~ 10 y (5 y 4 m)
EPC	11	3
Hemiplegia	14	4
Surgical treatment	11	4
Hemispherectomy	7	0
Death	1	1

interval between the onset age of epilepsy and that of frequent seizure recurrences (daily seizures developed) were 1 year and 4 months in the former and 3 years and 4 months in the latter. The seizures affected the left side of the body in 14 patients (52%) and right side in the remaining 13 patients (48%). Fourteen of the 19 patients with CORP (74%) and 4 of the 8 patients with LOSP (50%) developed hemiplegia, either at the latest follow-up period or before epilepsy surgery. The average time from the onset age of epilepsy to the development of hemiplegia was 3 years and 5 years and 4 months, respectively. Thus, patients with CORP showed more frequent complications with EPC and hemiplegia than those with LOSP. Three patients with LOSP were accompanied by uveitis, ipsilateral to the involved hemisphere at 2 years before, at the period of, and at 6 years after epilepsy onset, respectively. One patient each with CORP and LOSP died of status epilepticus caused by infection at 7 years of age and of a sudden unknown cause at 17 years of age, respectively.

3.2. Immunological examinations

Serum or CSF autoantibodies against the *N*-methyl-D-aspartate glutamate receptor (NMDA-type GluR) ε2 subunit and its epitopes [11] were positive in 13 of the 18 patients (72%) and 6 of the 8 patients (67%), respectively (Table 1). CSF oligoclonal IgG banding was positive in one patient each. Serum cytokine levels were within the normal range in two patients with CORP, but were only measured during steroid therapy. CSF IL-6 was measured to be normal in one patient with LOSP.

3.3. Effect of immunomodulatory treatment

Immunomodulatory treatments including high-dose steroid therapy, high-dose intravenous immunoglobulin (IVIG) administration, and other immunomodulatory agents were tried in a total of 19 patients. They were initiated 4–96 months after the onset of epilepsy (Table 1). The high-dose steroid therapy in most cases was started with the intravenous administration of methyl-prednisolone (MP) for 3 consecutive days (MP pulse therapy) given twice or three times every other week, followed by oral prednisolone (1–2 mg/kg) over a period of a few to several months depending on the response. The high-dose IVIG therapy consisted largely of an initial administration of 200–400 mg/kg consecutively for 3 days, followed by the same single dose once a month for a few months depending on the response.

The high-dose steroid and high-dose IVIG therapies were tried in 14 and 12 patients, respectively. The duration of the one treatment course ranged from 1 to 4 months, depending on the response to treatment. The high-dose steroid therapy achieved more than a good response in 5 patients (36%), and transient response in 3 cases. The IVIG therapy achieved a more than good response in 4 cases (33%) and transient response in 3 cases (Fig. 1). The high-dose steroid and IVIG therapy appeared better in response for those with CORP and LOSP, respectively despite no statistical significance ($P > 0.05$). Azathioprine, INF-α, cyclosporine, and ganciclovir were tried in a few patients without appreciable effects. Three patients have now been placed on tacrolimus, but one of them recently underwent hemispherectomy because of neurological deterioration and continuous EPC, leading the patient to be confined to a wheelchair.

3.4. Neuroimaging characteristics

MRI demonstrated progressive atrophy of the left hemisphere in 11 patients and of the right hemisphere in 14, although 2 pathologically-proven RE patients showed no apparent hemispheric MRI lesions. SPECT and PET studies all supported the lateralization of the MRI and EEG findings. The evolutionary changes in the HR were evaluated in 9 patients (CORP: 6 cases;

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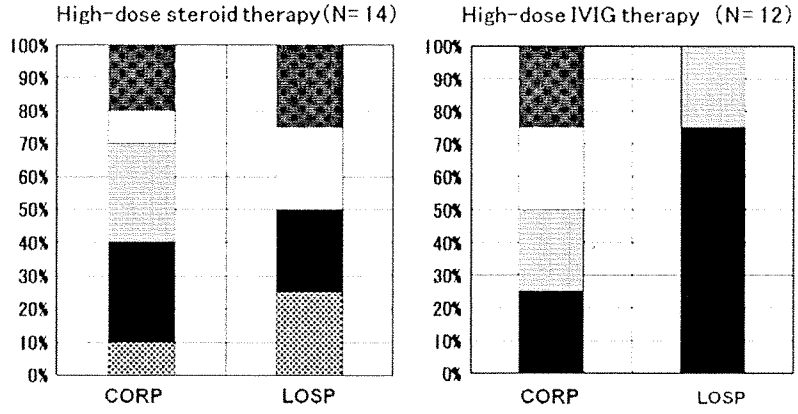

Fig. 1. Effectiveness of immunomodulatory therapy. Excellent, good, no improvement: more than 80% reduction, 50% to 80% reduction, and less than 50% reduction of the seizures, respectively. Transient improvement: more than 50% transient reduction of the seizures. Excellent ■, good response ▩, transient response ▤, poor response ■, aggravation ▩.

LOSP: 3 cases). The HR changes in the former showed a more rapid decline from the first examination than that in the latter, indicating a more rapidly progressive shrinking of the affected hemisphere in the former (Fig. 2).

3.5. *Response to epilepsy surgery*

Focal resection with or without multiple subpial transection and functional hemispherectomy was undertaken in 8 and 7 patients, respectively. The former procedure achieved a more than good response in 5 (63%) patients, although none of them became seizure-free. All 7 patients undergoing functional hemispherectomy have remained seizure-free.

4. Discussion

This study is the first Japanese nationwide cohort study involving 27 patients with RE. There have been a large number of investigations regarding various aspects of RE, all of which involved Caucasian patients. The clinical pictures, as well as progressive nature of the disorder in our patients recruited based on the proposed RE criteria, are consistent with those from previous studies. We can subclassify them into those with a childhood-onset rapidly progressive clinical course (CORP) compatible with classical RE, and those with a late-onset slowly progressive clinical course (LOSP) compatible with adult type RE [1,2,18,19]. The average time between the onset age of epilepsy and that of frequent seizure recurrence, and the mean period between the onset age of epilepsy and development of hemiplegia in our series were also similar to those of previous reports.

Bien et al. measured the hemispheric ratio (HR), in which the axial cross-section of the affected hemisphere is expressed in relation to the unaffected one, and quantitatively showed the progressive destruction of the affected hemisphere over time [2]. This method applied to 9 of our patients demonstrated the difference in the HR between those with CORP and those with LOSP, and seemed to be useful for the evaluation of treatment.

Regarding the pathogenesis of RE, since Rogers et al. [9] identified the autoantibody against the ionotropic glutamate receptor GluR3 in the serum of RE patients, the autoimmune process underlying RE has received growing attention. Subsequently, autoantibodies against GluRε2, munc-18, and glial cells have been demonstrated in the serum of RE patients [10,11,13]. We also found GluRε2 antibody in the serum or CSF of roughly 2/3 of our patients at either the onset of epilepsy or in the middle of the clinical course [20]. However, the specificity of these autoantibodies as a primary etiology remains unclear because they were also found in other noninflammatory focal epilepsies or nonspecific encephalitis. Recently, interest is growing toward cell-mediated rather than humoral immunity, with the speculation that cytotoxic T cells destroy neurons through the release of granzyme-B, leading to the progressive destruction of the hemisphere [12,20]. Thus, the notion of a previous infection or vaccination prior to the onset of RE triggering the autoimmune process of the disorder has been challenged, although we could identify these episodes in only one third of our series [21]. However, among them, there were 3 patients with LOSP experiencing uveitis ipsilateral to the affected hemisphere, either long after or before the onset of epilepsy. Uveitis is caused mostly either by viral infections or an autoimmune process in those with systemic autoimmune disorders. Together with previous case reports, the combination of uveitis and RE is not a coincidental event but indicates the same autoimmune process involving both the uveal tract and ipsilateral hemisphere with other sys-

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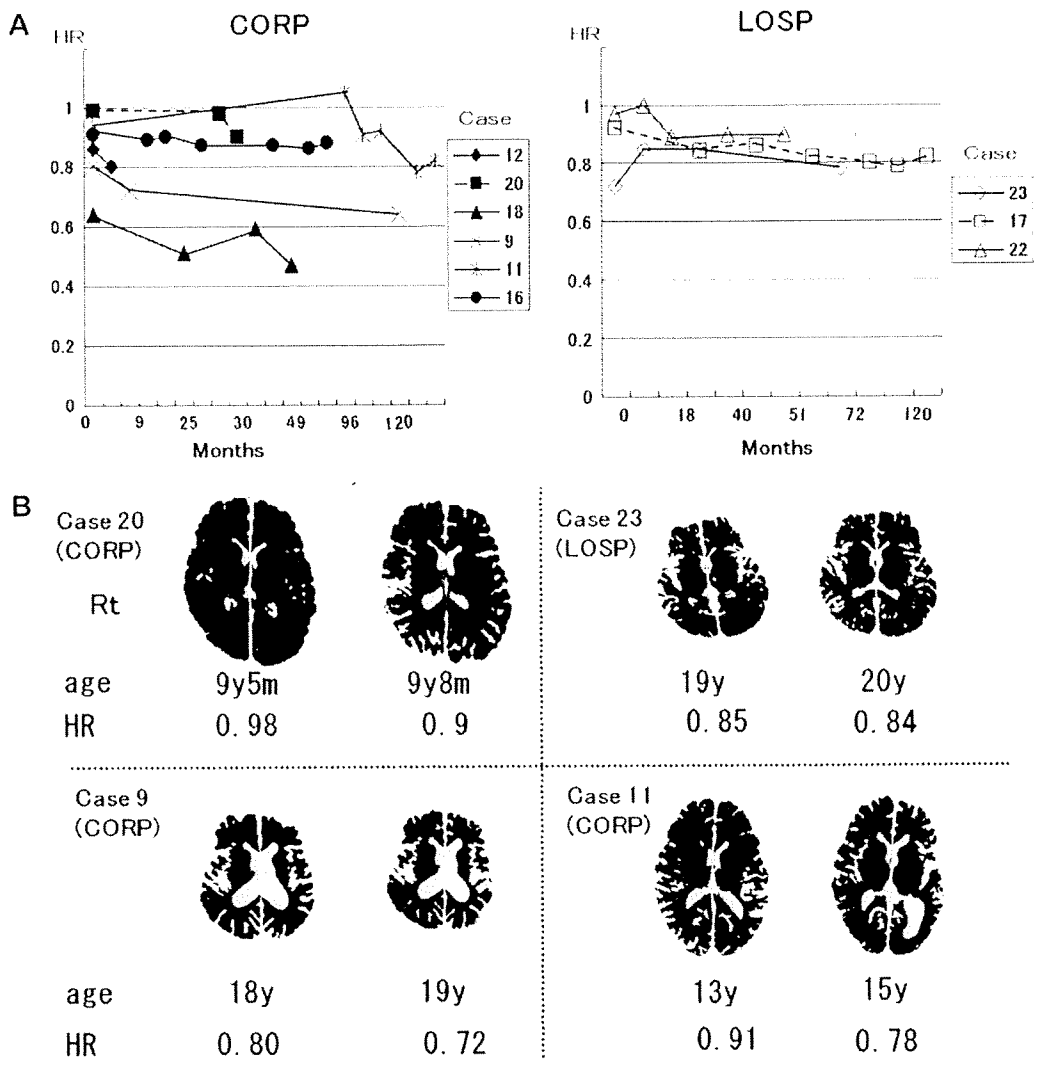

Fig. 2. Serial changes in the hemispheric ratio (HR). (A) Serial HR changes depicted as a sequential line graph for each RE type. (B) Typical examples of HR. Case letters correspond to those of Fig. 2A.

temic autoimmune disorders [14,22]. There must be various factors contributing to the onset of RE, in which the mutation of *SCN1A* causing severe myoclonic epilepsy in infants or generalized epilepsy with febrile seizure plus may be a candidate [17].

Thus, various immunomodulatory treatments have been attempted in patients with RE based on the autoimmune hypothesis. Promising results of high-dose intravenous immunoglobulin (IVIG) treatment have recently been demonstrated in patients with adult-onset RE [23,24]. Leach et al. demonstrated sustained improvement in patients following the long-term usage of high-dose IVIG, despite resistance to steroid treatment in these patients [23]. High-dose steroid treatment has been attempted more frequently than IVIG therapy, with inconsistent results [25–27]. In our results, the high-dose steroid and IVIG therapies brought a better than good response in approximately one third of cases, respectively. The high-dose steroid therapy was more effective for those with LOSP than the IVIG therapy, while the latter therapy appeared to be more beneficial in those with CORP than the former therapy. However, these two therapies could not fully control the seizures nor halt the neurological deterioration, even in responding cases. Tacrolimus has been shown to have a beneficial effect on reducing the progression of hemiatrophy, but does not improve the seizure outcome [28]. In our series, there were 3 patients taking tacrolimus, although one of them finally underwent hemispherectomy due to neurological deterioration and daily EPC up to the level of becoming unable to walk. The effect of tacrolimus will remain undetermined until long-term follow-up data

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from a larger number of patients are provided. The effect of immunomodulatory therapy for RE remains equivocal in part due to a limited number of case trials, the differences in treatment regimens, and the slowly progressing and relapsing-remitting clinical course of this disorder itself, hampering a precise assessment of efficacy [1]. In the meantime, these immunomodulatory treatments should be initiated cautiously and stopped when no meaningful improvement is recognized.

Regarding surgical treatment, functional hemispherectomy has been shown to be the final and best option for condition, although this procedure is only possible when hemiplegia has stabilized [7]. In addition, this procedure should be cautiously considered when RE affects the dominant hemisphere. In our series, the hemispherectomy was performed on only non-dominant right hemisphere in all 7 patients. If dominant left hemisphere is affected, we have to wait for this radical procedure until the language center transfer to the non-dominant hemisphere, which can be ascertained by Wada test or fMRI study [29]. Although early hemispherectomy is recommended to reduce the involvement of the unaffected hemisphere by some, a consensus regarding when to introduce hemispherectomy has not been determined globally [8,30]. The hemispheric ratio may become one of the objective markers to introduce hemispherectomy.

In this study, we were able to identify a significant number of patients with RE in Japan, who showed a similar clinical course as well as neuroimaging findings with those reported from Western countries, and have received appropriate immunomodulatory as well as surgical treatment.

Disclosure of conflict of interest

We have no conflicts of interest.

Acknowledgement

This study was supported by the Japan Epilepsy Research Foundation. We confirm that we have read the Journal's position regarding issues pertaining to ethical publication, and affirm that this report is consistent with those guidelines.

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特集 てんかん医療の進歩

てんかん外科の進歩

大槻泰介

Key Words
epilepsy surgery, surgical approach, resective surgery, palliative surgery, electrical stimulation

1 はじめに

てんかんの外科治療は，19世紀末以来脳波の発見とともに発展したが，昨今のMRI，PET，SPECTおよびMEGなどの新しい診断機器の導入によりてんかん原性病変を同定する精度が飛躍的に向上し，また手術の技術的進歩もあり，現在てんかん外科の手術適応は，成人から乳幼児に至るまでのさまざまな症候性てんかんに拡大している（表1）。

一方てんかんの病態について，繰り返されるてんかん発作により惹起されるさまざまな神経生物学的脳機能異常や認知・心理・社会面での影響に関し理解が深まるにつれ，外科治療の目的に関しても，てんかん発作の消失はもちろん，発作の抑制により得られる発達障害や自立・就労状況の改善について注目が集まるようになってきている。

2 てんかん外科の始まり

てんかん発作は脳神経細胞の過剰で同期した異常発射に由来するとされるが[17]，この基本概念に基づいて大脳皮質灰白質の"発射病巣"を切除することを目的として行われたてんかん外科手術は，1886年にHughlings JacksonとVictor Horsleyの共同作業で行われた部分運動発作を伴う外傷性てんかん患者に対する運動野近傍の瘢痕切除が最初とされる[2]。爾来120年間，てんかん外科の基本命題は，この"てんかん原性領域"[24]をいかに同定し切除するかという課題であり続けてきた。

3 てんかん原性領域の探索

てんかん外科におけるてんかん原性領域同定の歴史は，1）発作症状の時代（1886年以降），2）脳波の時代（1940年代），3）神経画像の時代（1980年代）の3期に分けられる[43]。第1期の発作症状の時代には，片側性の部分運動発作や発作後の運動麻痺などの神経兆候を手がかりとして，運動野近傍の"発射病巣"の存在を推定し手術が選択された[25]。次いで脳波の導入により，術中皮質脳波記録（34）や深部電極を用いたstereoencephalography（SEEG）[8]，さらには硬膜下電

Progress in neurosurgical approach for intractable epilepsies
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表1　てんかん外科手術の主な適応

切除手術（根治手術）	内側側頭葉てんかん（海馬硬化，腫瘍性病変を伴う）
	病変を伴う新皮質てんかん
	腫瘍性病変・血管性病変
	限局性皮質異形成（Focal cortical dysplasia）
	瘢痕脳（Ulegyria）
	片側巨脳症
	スタージ・ウエーバー症候群
	ラスムッセン脳炎
脳梁離断（緩和手術）	脱力転倒発作を呈する症候性てんかん

極留置による頭蓋内脳波記録[23]に至る過程を経て，電気生理学的手法である脳波がてんかん原性領域同定の主流に位置づけられた。特に発作時ビデオ脳波同時記録が1970年代に導入され発作症状と脳波の対比が可能となると，術中の発作間欠期脳波記録にかわり，慢性頭蓋内電極留置下の発作時脳波記録による発作起始領域の同定が，てんかん外科戦略上重要な地位を占めるようになった[36]。

さらに第3期に当たる現在，MRIの導入により皮質異形成や海馬硬化などの組織学的異常が画像で同定可能となり[12]，またPET・SPECTにより発作時および発作間歇期のてんかん脳の代謝循環動態が明らかとなったことで[5,15]，てんかん原性領域を構成する，てんかん原性病変，発作起始域，発作症状発現域，機能低下域，および興奮域などの病態が，画像として描出されるようになった。

4　てんかん外科と脳機能局在

てんかん外科の歴史は脳機能局在の発見の歴史でもある。Horsleyの手術自体，当時の動物実験における電気刺激による運動野の発見に支えられたものであった。てんかん外科の最初の標的は中心前回であったが，術中皮質刺激の知見はKrause，Foersterを経てPenfieldに引き継がれ[25]，ヒトの一次知覚運動野の脳機能地図が完成されるとともに，術中皮質刺激により大脳半球および島皮質におけるさまざまな運動・知覚反応や経験反応(experiential response)が誘発され，脳機能の局在と発作症状に関する知見が深まった[34]。

さらにその後，頭蓋内電極留置による皮質刺激により，一次知覚運動野，捕捉運動野，視覚野，言語野などが詳細に同定され[23]，側頭葉てんかん，前頭葉てんかん，頭頂葉・後頭葉てんかんなど，脳の領域ごとに特徴的な発作兆候が明らかとなると，発作症状の解析がてんかん分類[35]上も重要な地位を占めるようになった。また最近では，記憶・自己身体イメージ・精神症状など，より高次の脳機能に関連した発作症状の理解が進んでいる[6,14]。

一方，発作時SPECTの解析により，てんかん発作の起始と伝播に伴うニューロネットワークを介する脳血流動態の変化が明らかになってきた[38]。特に発作時SPECT像と発作間歇期SPECT像の差分をコンピュータ処理しMRI上に表示するSISCOM（subtraction ictal SPECT coregistered to MRI）[27,30]の出現により，従来視覚的には検出し難かった皮質・皮質下のさまざまな領域における脳血流変化が解析できるようになり，発作起始領域の検索だけでなく，意識障害の発現機序など，発作症状発現の病態の理解に貢献している[7]。

また脳機能局在の理解は，てんかん原性領域を推定する根拠となるが，同時に手術による神経障害発生を予見する手がかりともなる。ワダ・テスト(アミタール・テスト)による言語および記憶の優位側判定は，側頭葉てんかんの外科

治療における重要な術前評価とされ，術後の言語および記憶障害の問題は手術アプローチとの関連で長く議論されてきた[10,19]。てんかん外科においては神経障害の発生を未然に防ぐことが肝要であり，一次知覚運動野，言語野，視覚野などのeloquent cortex近傍の手術においては，硬膜下電極による皮質刺激や術中刺激あるいは脳磁図やfMRIを用い脳機能地図の作成を行うことが基本となる。

またてんかんはてんかん発作だけでなく発作間欠期の病態にも特徴づけられる疾患であり[17]，てんかん外科手術の最終目的は，てんかん発作の消失による患者のQOLの改善にある[22]。その観点から，言語，記憶，認知，心理，発達など，QOLに関連する神経心理評価は，てんかん外科の術前術後評価プログラムにおいて重要な地位を占めている。

5 切除手術と緩和手術

てんかん外科手術の目的は，新たな神経障害を起こすことなくてんかん原性領域を完全に取り除き，てんかんを根治することにある。しかし一方，てんかん原性病変の局在が明らかでない場合，あるいはその切除が困難な難治てんかん症例に対しては，発作の軽減・緩和を目的とした手術が考案され，前者を切除外科(resective surgery)，後者を緩和外科(palliative surgery)と呼んでいる。

切除外科手術の基本は，脳回単位で病変を含む灰白質を除去し残存脳回や白質は循環障害を来さないよう温存することにある。また病変の範囲が広く広範な皮質切除が必要な症例に対しては，多葉離断(multilobar disconnection)や半球離断術(hemispherotomy)など，血管系を温存したまま正常脳組織より病変脳組織を切り離す離断手術(disconnective surgery)も開発されている[11,12]。

切除外科の対象となる病変には，DNT，gangliogliomaなどの腫瘍性病変，海馬硬化，皮質異形成，瘢痕脳回，海綿状血管腫，スタージウエーバー症候群，片側巨脳症，ラスミュッセン脳炎などがある。海馬硬化を伴う内側側頭葉てんかん，あるいは腫瘍性病変，海綿状血管腫などの限局性の器質病変を伴う症例では良好な手術予後が得られており，80%以上の症例で術後の完全発作消失が期待できる。また皮質異形成は，病変自体にてんかん原性があるとされるが[73]，MRI上示される異常域の外にも病理学的異常が広がっている可能性があるため，切除領域の設定には慢性頭蓋内脳波記録が必要とされる[43,26]。一方MRI上病変を認めない場合や摘出標本にグリオーシス以外の病理学的異常を認めない場合，切除手術の予後は良好ではない[45]。

6 小児のてんかん外科手術

小児の難治てんかんは，発達脳にてんかん性脳機能障害を及ぼし，乳幼児では破局てんかん(catastrophic epilepsy)と呼ばれる重篤な病態をもたらす[44]。てんかん性病変を切除し発作から開放することで，術後の機能獲得を期待することができるが，小児特に乳幼児においては，発作症状や脳波所見は全般化する傾向があり，臨床像からてんかん性病変の局在を推定することはも容易ではない[1]。また複数の脳葉にまたがる広汎な病変を伴う場合も少なくないが，離断手術を選択することで比較的少ない侵襲で発作の完治を得ることが可能であり[11,12]，乳幼児期から積極的に切除手術が行われるようになった。

7 緩和外科手術

緩和外科の歴史を振り返ると，その基本的概念として，1)発作伝播路の遮断，2)脳全体の発作閾値の上昇，3)てんかん原性領域に対する低侵襲治療，の3群にわけられる。脳梁離断[3,26]や古典的定位脳手術，あるいは最近欧米中心に臨床治験が行われている脳深部刺激治療

(DBS)[18]は，神経路を遮断することで神経路を介した発作の全般化を防ぐことを目的としている。また，迷走神経刺激[21]は，迷走神経核を上行性に刺激することで脳全体の発作閾値の上昇を期待するものであり，一方，MST[28]や海馬電気刺激[42]，あるいはガンマナイフ治療[37]は，てんかん原性領域は同定するが，切除することなく発作閾値を上げる試みといえる。

以下代表的な緩和手術につきその概要を述べる。

1. 脳梁離断術

脳梁離断は，van Wagnenらの1940年の報告以来，大脳半球間の交連線維を切断することで，てんかん性活動の半球間の伝播を抑制し，大脳皮質におけるてんかん性活動の両側性同期(bilateral synchrony)を防ぎ，二次性全般発作を緩和することを目的として行われてきた[42]。

脳梁離断の手術適応は，脱力，強直，ミオクローヌス，強直間代など両側性の運動症状を呈する二次性全般発作が主な対象とされる。脳梁離断術では発作消失が期待できるのは7.0％と少ないが，脱力による転倒発作の治療予後は良好である[26]。

2. 脳深部刺激術

てんかんに対する脳刺激治療は，これまで小脳[9]，視床前核(anterior nucleus)[18]，視床正中中心核(centromedian nucleus)[39]，視床下核(subthalamic nucleus)[4]，および海馬[40,41]を目標とした刺激治療が報告されているが，その有効性についてはなお検証が必要とされている。

3. 迷走神経刺激術

迷走神経刺激術は，頸部の迷走神経に電極を装着し間歇的に電気刺激を加えることで発作の改善を目的とする治療法であるが，欧米では，すでに一般的なてんかん外科の手術手技とされており[16,21]，わが国でも近日中に導入される予定である。迷走神経は，解剖学的にはその約80％が求心性線維であり，主に延髄の孤束核に至り，さらに視床下部，扁桃核，視床，島皮質などに投射する。

迷走神経刺激の適応は，薬物治療では発作の抑制が困難な部分てんかんで，切除手術など標準的なてんかん外科の適応がないことが確認された症例とされる[16]。刺激条件は30秒間の刺激を5分間隔で行う方法が最適とされるが，刺激によって反回神経に至る有髄神経(Aα)が刺激され間歇的に嗄声が生ずる。

4. 軟膜下多切術

軟膜下多切術は，皮質内の水平方向の神経線維を離断することで，神経機能単位の柱状構築を温存しつつ，皮質内の異常な神経活動の同期を防ぐ手術手技であり，一次知覚運動野，言語野，視覚野などのeloquent cortexにおいて，機能を温存しかつてんかん原性を抑制することを目的として行われる[28]。eloquent cortexにてんかん原性を有する大脳皮質てんかん，ランドクレッフナー症候群への適応例が報告されている[29,38]。術後早期の発作抑制は比較的良好であるが，数年以内に2割近く再発するとの報告もある[31]。

8 てんかん外科治療の目的

てんかんの外科治療の目的は，小児においては「発達障害の予防と改善」，成人においては「自立と就労の促進」にある。難治性てんかんは，長期にわたり繰り返すてんかん発作により，発達脳においてさまざまな脳機能障害を惹起し，これに教育・学習の機会が奪われることによる心理社会的障害が積み重なる病態を示す。また成人においては就業の機会が失われることによる社会経済学的損失も計り知れない。てんかんの診断と治療においては，手術で治療可能なてんかん(surgically remediable epililepsy)の早期発見と早期治療が重要とされる。

9 てんかん外科の需要と供給

一般に，てんかんの有病率は人口1,000人あたり約5人と推定され[1]，このうち約20％は少

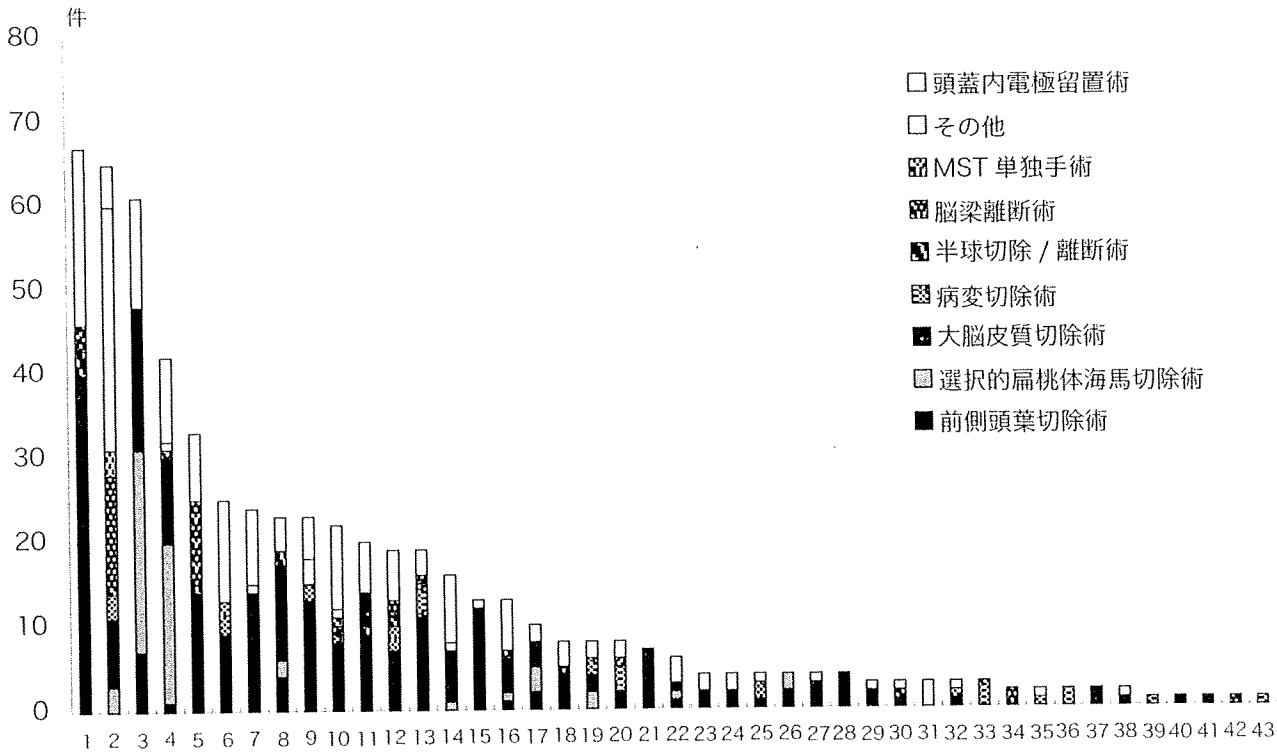

図　日本における各施設ごとのてんかん外科手術件数（2004年1月～12月：合計43施設，586件）（文献32より改変）

なくとも月1回以上の発作を呈し[2]，これらの難治性てんかんの60%は部分てんかんで潜在的な外科手術の対象となるとされる[4,5]。したがって，わが国における潜在的外科適応患者は約72,000人と推定され，これに毎年新たに発症する難治性てんかん患者を加えると，わが国では少なくとも年間2,000件以上のてんかん外科手術が必要と推測される。しかし実際には，わが国のてんかん外科手術の件数は年間500例前後で[32]（図），これは韓国や英国の約半分にすぎず，必要と推測されるてんかん外科手術の需要にはるかに及んでいないのが現状である。このことは，わが国では多くの難治てんかん患者が本来必要とする医療を受けられずに，さまざまな発達，教育，就業などにおける困難に遭遇していることを示すものと推測される。

10 おわりに

てんかん外科の歴史は，発作症候学，脳波学，神経心理学および画像診断学の進歩に支えられており，てんかん外科手術を行うにあたっては，発作時ビデオ脳波記録，慢性頭蓋内脳波記録，神経心理評価，神経画像などの診断技術を駆使し，てんかん原性領域を同定し根治することで，患者のQOLを改善することが求められる。

一方，わが国のてんかん外科は，いまだ本来の需要を満たしているとはいえず，多くの患者が発達，教育，就業などの生活上の困難に遭遇していると推測される。てんかん外科治療で治癒可能な難治てんかん患者の早期発見・早期治療の推進が課題である。

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