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Current Topics in Epilepsy Surgery

Naotaka USUI[1]

[1]*National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Aoi-ku, Shizuoka*

Abstract

This article reviews the current topics in the field of epilepsy surgery. Each type of epilepsy is associated with a different set of questions and goals. In mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS), postoperative seizure outcome is satisfactory. A recent meta-analysis revealed superior seizure outcome after anterior temporal lobectomy compared with selective amygdalohippocampectomy; in terms of cognitive outcome; however, amygdalohippocampectomy may be beneficial. In temporal lobe epilepsy with normal magnetic resonance imaging (MRI), postoperative seizure outcome is not as favorable as it is in MTLE with HS; further improvement of seizure outcome in these cases is necessary. Focal cortical dysplasia is the most common substrate in intractable neocortical epilepsy, especially in children, as well as in MRI-invisible neocortical epilepsy. Postoperative seizure-free outcome is approximately 60–70%; further diagnostic and therapeutic improvement is required. Regarding diagnostic methodology, an important topic currently under discussion is wideband electroencephalogram (EEG) analysis. Although high-frequency oscillations and ictal direct current shifts are considered important markers of epileptogenic zones, the clinical significance of these findings should be clarified further. Regarding alternatives to surgery, neuromodulation therapy can be an option for patients who are not amenable to resective surgery. In addition to vagus nerve stimulation, intracranial stimulation such as responsive neurostimulation or anterior thalamic stimulation is reported to have a modest seizure suppression effect. Postoperative management such as rehabilitation and antiepileptic drug (AED) management is important. It has been reported that postoperative rehabilitation improves postoperative employment status. Pre- and post-operative comprehensive care is mandatory for postoperative improvement of quality of life.

Key words: epilepsy surgery, mesial temporal lobe epilepsy, cortical dysplasia, broadband electroencephalogram

Mesial Temporal Lobe Epilepsy (MTLE)

Epilepsy surgery for MTLE and focal epilepsy with localized lesion are recognized as an established treatment for medically intractable patients. A randomized controlled trial (RCT) of temporal lobe epilepsy (TLE) surgery revealed that surgical therapy is superior to medical therapy alone in terms of seizure outcome and quality of life.[1)] Standard anterior temporal lobectomy (ATL) (Fig. 1A) has been reported to result in seizure freedom rates of 70% or better.[1,2)] Since selective amygdalohippocampectomy (SAH) (Fig. 1B) was first reported by Wieser and Yasargil in 1982,[3)] there has been a great deal of discussion about optimal surgical procedures, both from the standpoint of seizure outcome and from that of neuropsychological outcome. SAH may be equivalent to ATL as far as seizure outcome is concerned,[4–7)] and is often superior in terms of neuropsychological performance after surgery.[5,6,8)] A recent meta-analysis reported by Josephson et al. revealed superior seizure outcome after ATL compared to SAH.[9)] Specifically, the outcomes of the 1,203 patients in the 11 studies demonstrated that participants were statistically more likely to achieve an Engel class I outcome after ATL than after SAH (risk ratio 1.32, 95% confidence interval 1.12–1.57; $p < 0.01$). The summary risk difference of 8% translated to a number needed to treat 13 for 1 additional patient to achieve an Engel class I outcome after ATL. The author concluded that improved seizure outcome must be balanced against the neuropsychological impact of each procedure.

It has been thought that failure to achieve seizure freedom after temporal lobe surgery is due to contralateral epileptogenesis, dual pathology, or extratemporal foci. These factors cannot explain

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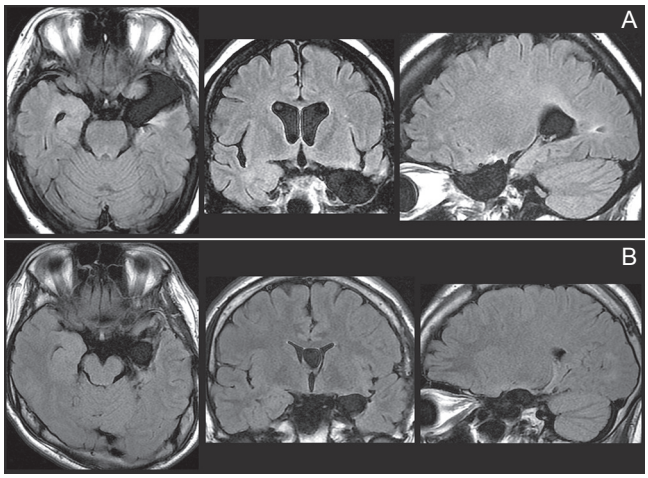

Fig. 1 Postoperative magnetic resonance imaging showing the extent of resection after temporal lobe surgery. A: Standard anterior temporal lobectomy and B: selective amygdalohippocampectomy.

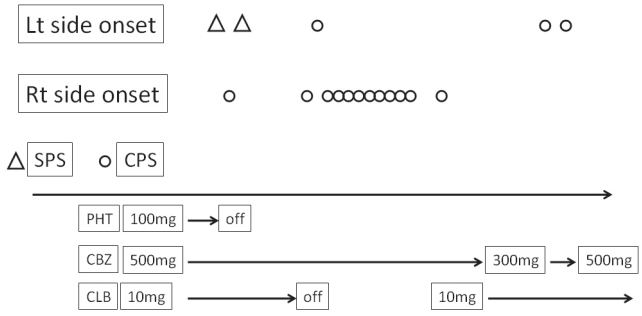

Fig. 2 Seizure diagram during intracranial electroencephalogram monitoring and antiepileptic drug. Seizures originating from the right side were more frequently recorded than those from the left. Note that clusters of right-onset seizures occurred after discontinuation of CLB. CBZ: carbamazepine, CLB, clobazam, CPS, complex partial seizure, Lt: left, PHT: phenytoin, Rt: right, SPS: simple partial seizure.

all surgical failures, however. There is no apparent difference in the clinical characteristics or study results between patients with favorable and unfavorable postoperative seizure outcomes. Recently, Keller et al.[10] studied 87 patients with MTLE who underwent SAH (47 subsequently seizure-free, 40 with postoperative seizures) and 80 healthy controls, investigating the relationship between imaging variables and postoperative seizure outcome. All patients had unilateral temporal lobe seizure onset and ipsilateral HS as the only brain lesion. The results showed that patients with postoperative seizures had significant atrophy of the bilateral dorsomedial and pulvinar thalamic regions, and significant abnormalities of the diffusion tensor imaging (DTI)-derived thalamotemporal probabilistic paths. They concluded that patients with bihemispheric alterations of the thalamotemporal structural network may represent a subtype of MTLE that is resistant to temporal lobe surgery.

While postoperative seizure outcome of MTLE with HS is favorable, that of TLE with normal magnetic resonance imaging (MRI) is less so. We previously reported 12 patients with MTLE with no specific histological abnormality.[11] Intracranial EEG was performed in all patients, revealing that bitemporal seizures are common in MTLE with no histological abnormality. SAH was performed in all patients, and seizure outcome was classified as Engel class I in seven patients, class II in three, class III in one, and class IV in one. SAH was effective even in cases with bitemporal independent seizure onset. In three patients, seizures originated more frequently from the side contralateral to the resection than from the resection side, yet the seizure outcome in these patients was relatively favorable. Several studies of bitemporal epilepsy have used the distribution of seizure origin to determine the side on which surgery will be performed. This alone is not a reliable determinant, however. Fig. 2 shows a seizure diagram during intracranial EEG monitoring in one patient with MTLE with normal histopathology. Seizures originating from the right side were more frequently recorded than were those from the left side. After medication withdrawal, however, seizures began to cluster on the right side. Interictal IMP-SPECT showed hypoperfusion of the left temporal lobe. After left SAH, the patient had several seizures within 1 year after surgery, but subsequently became seizure-free for more than 6 years. In determining the side of surgery, the situation in which the seizures were recorded (medication withdrawal, seizure clusters, or seizures that are atypical for the patient) should be taken into consideration. Moreover, the functional reserve of the contralateral temporal lobe should be confirmed by functional neuroimaging and/or WADA test. Recently, Aghakhani et al. systematically reviewed the literature regarding epilepsy surgery in patients with bilateral temporal lobe seizures[12] and found that a significantly higher proportion of patients achieved good seizure outcomes when intracranial EEG showed unilateral TLE (67%) than when it showed true bilateral TLE (45%). In patients with bilateral TLE, the degree of seizure lateralization during intracranial EEG is not associated with seizure outcomes, and should have a limited role in selecting the side of surgery.

Hippocampal transection (HT) was introduced to prevent postoperative memory decline in patients

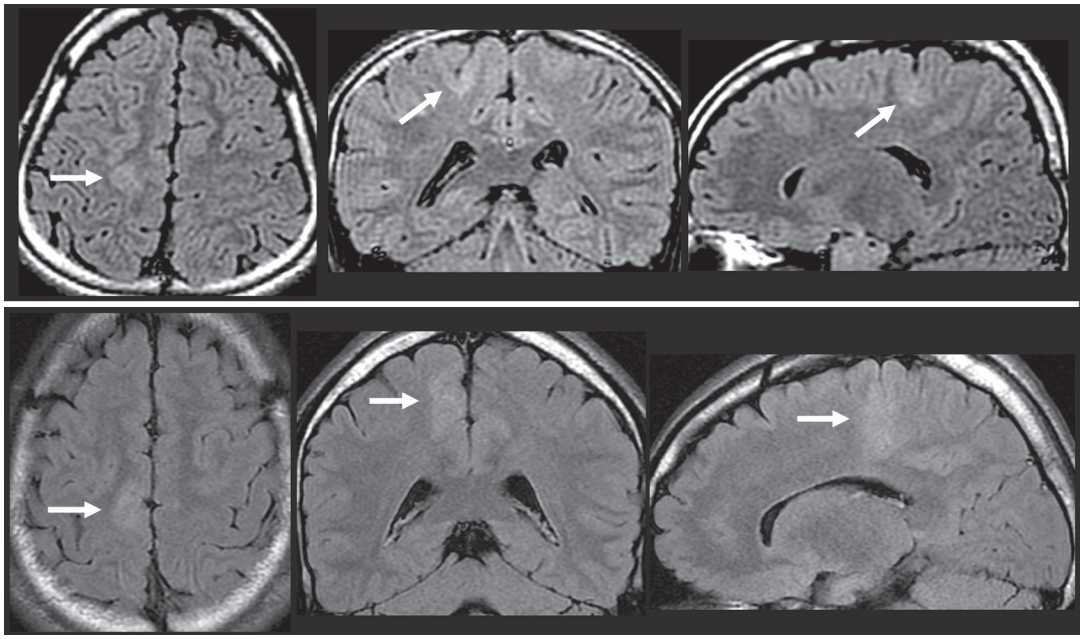

Fig. 3 Fluid attenuation inversion recovery-magnetic resonance imaging of two patients with perirolandic focal cortical dysplasia. *White arrows* indicate hyperintensity areas which represent the presence of focal cortical dysplasia located mainly in the primary motor area.

with MTLE without hippocampal atrophy or sclerosis. Uda et al. reported 37 patients with MTLE without hippocampal atrophy or sclerosis who underwent HT.[13] In HT, the longitudinal hippocampal circuits of epileptic activities are disrupted by transection of the pyramidal layer of the hippocampus. Follow-up periods ranged from 12 months to 94 months (median 49 months). Engel class I was achieved in 25 patients (67.6%). On the language-dominant side, memory function indices (verbal memory, nonverbal memory, and delayed recall) showed no significant change.

As a minimally invasive surgery, laser ablation of mesial temporal structures has been reported by a group at Emory University.[14] MRI-guided stereotactic laser ablation uses small applicators amenable to stereotactic delivery. Heating is dependent on source wavelength such that a source laser can be chosen to produce rapid and localized heating of tissue with sharp boundaries at relatively low powers. Real-time laser output and tissue ablation are possible. In MRI-guided stereotactic laser amygdalohippocampectomy (SLAH), the target area is destroyed by placing a saline-cooled laser applicator in the amygdalohippocampal structures from an occipital trajectory under general anesthesia, mimicking the effects of SAH. Other researchers as the same institute compared the neuropsychological outcome of SLAH with that of traditional surgery.[15] They showed that naming and recognition functions can be spared in TLE patients undergoing SLAH, while short-term seizure outcome was similar. This procedure may become a viable option for patients with MTLE if long-term seizure outcome is also similar.

Cortical Dysplasia

Cortical dysplasia is the main pathological substrate of intractable neocortical epilepsy, and the most common etiology in children undergoing epilepsy surgery. Presurgical evaluation of patients with intractable epilepsy and cortical dysplasia is still challenging. About 60% of patients with cortical dysplasia are seizure-free after surgery, with complete resection yielding a much higher rate of seizure freedom (80%) compared to incomplete resection (20%). In some patients, cortical dysplasia is located in the vicinity of the perirolandic area (Fig. 3). MRI is negative in approximately 30% of cases.[16] The advent of higher-field magnets at $\geq$ 3T, combined with the use of phased array coils has resulted in improved image signal-to-noise and contrast-to-noise ratios. Moreover, computer-based models of cortical thickness, blurring, and tissue intensity derived from three-dimensional T_1-weighted images and combined into a single composite map increased the sensitivity of visual identification of histologically proven focal cortical dysplasia by 30% relative to conventional MRI, while maintaining high specificity.[17] Future therapeutic challenges include

preoperative identification of subtle type I dysplasia and improvement of surgical technique for lesions in the vicinity of eloquent areas.

Long-term studies on the outcome of focal cortical dysplasia surgery are rare. Krsek et al. studied 149 patients with histologically confirmed focal cortical dysplasia with at least 2 years of postoperative follow-up. Engel class I outcome was obtained in 55% of patients. The only significant predictor of surgical success was completeness of surgical resection.[18] Fauser et al.[19] recently reported long-term seizure outcome of 211 patients with focal cortical dysplasia. After 1 year, Engel class I outcome was achieved in 65% of patients and the percentage of seizure-free patients remained stable over the following (up to 12) years. Complete resection of the assumed epileptogenic area, lower age at surgery, and unilobar localization were positive prognostic indicators of long-term seizure freedom.

Kimura et al.[20] studied developmental outcome after surgery for early-onset epilepsy in patients with focal cortical dysplasia treated at our institute. Seventeen patients with epilepsy onset prior to 3 years of age were selected. Epilepsy surgery effectively controlled seizures in 58.8% of focal cortical dysplasia patients with early-onset epilepsy, and preserved or improved development in 82.3%. Residual seizures after surgery and lower developmental quotient-intelligence quotient (DQ-IQ) before surgery might be potential risk factors for poor development after surgery. Engel class I patients with lower presurgical DQ-IQ were observed to have caught up in mental age 2 years after surgery.

Broadband EEG

The development of digital EEG machines has enabled us to analyze a very wide range of EEG activities. In particular, high frequency oscillations (HFOs) are often reported in the context of epilepsy surgery. A high sampling rate, usually faster than 500 Hz, is necessary for recording HFO. Akiyama et al.[21] analyzed 28 pediatric patients who underwent extraoperative intracranial video-EEG monitoring prior to focal resection, and reported that more thorough resection of regions with high-rate fast ripples was significantly correlated with better seizure outcome. Similarly, Jacobs et al.[22] studied 20 adult patients, and concluded that good surgical outcome is more strongly correlated with the removal of HFO-generating tissue than with that of spike-generating areas or the seizure onset zone (SOZ).

We used a very high sampling rate of 10 kHz and reported the presence of very high frequency oscillations (VHFOs) (faster than 1,000 Hz) in intractable neocortical epilepsy.[23] The VHFOs were detected in highly localized cortical regions (one to four subdural macroelectrodes in each individual patient). The amplitude of VHFO is very low (3.5–29.4 μV), and their duration is very short (2–226 ms). The VHFO appears intermittently in the interictal and preictal states (Fig. 4A), and become sustained after ictal onset (Fig. 4B). We studied 13 patients with neocortical epilepsy who underwent subdural electrode implantation, had at least one seizure recorded at a 10-kHz sampling rate and were followed for more than 2 years postoperatively. The extent of resection was determined based on the SOZ and the irritative zone, structural lesions, and functional areas. Areas showing VHFO or HFO were not taken into consideration. The presence of VHFO was correlated with favorable outcome and the areas with VHFO were completely resected. Resection of HFO and SOZ was not correlated with seizure outcome. Ictal VHFO may be a more specific marker than ictal HFO or SOZ for identifying the core of the epileptogenic zone.[24]

Many questions regarding HFO remain unanswered, however. The term "HFO" can refer to both pathological and physiological phenomena of diverse origin.

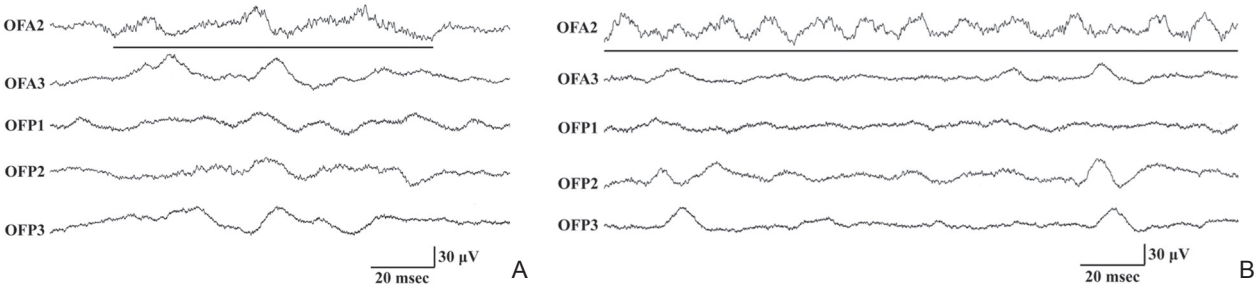

Fig. 4 A: Intermittent VHFO in preictal state at OFA2 electrode (less clearly seen at OFP2 electrode). Low-pass filter: 3 kHZ, time constant: 0.001 sec. B: Sustained VHFO after seizure onset at OFA2 electrode. Sustained VHFO superimposed over slower rhythmic activity. Low-pass filter: 3 kHZ, time constant: 0.001 sec. Note calibration. VHFO: very high frequency oscillation.

Physiological HFO are believed to be involved in memory consolidation. Although ripples (80–200 Hz) are mainly physiological while fast ripples (> 200/250 Hz) are mainly pathological, we cannot distinguish pathological HFO from physiological ones with sufficient accuracy based on frequency range alone. A reliable method of distinguishing them clinically is needed so that pathological HFO can be used as biomarkers for epileptogenicity.

Ictal direct current (DC) shifts have also received attention recently. Kanazawa et al.[25] studied the temporal-spatial characteristics of ictal DC shifts (or infraslow activity) and HFO in 16 patients with intractable focal epilepsy who underwent intracranial EEG recording. Either ictal DC shifts or HFO were observed in more restricted areas compared to conventional ictal changes. The same study also reported that ictal slow shifts preceded HFO, and proposed that this finding may suggest an active role of glia in seizure generation.

In intracranial EEG recordings, we identified a distinct pattern of brain activity in three patients with refractory focal epilepsy characterized by very early occurrence (8 min 10 sec to 22 min 40 sec prior to clinical seizure onset), periodic appearance of slow negative baseline shift, long interpeak interval (40–120 sec), and disappearance after clinical seizure. We named this activity "very low frequency oscillation".[26] Although the pathophysiology of this activity pattern is unknown, a better understanding of it in the future may yield new insight concerning epileptogenesis and the prediction of epileptic seizures.

Neuromodulation Therapy for Epilepsy

The modest seizure suppression effect of vagus nerve stimulation (VNS) was confirmed by two RCTs.[27,28] While VNS is not a curative therapy, more than 50% seizure reduction is reported in approximately 50% of patients after 2 years of treatment.[29] The VNS has been suggested to improve attention, cognition, behavior, mood, and quality of life independently of the reduction in seizure burden.[30] Although it has been suggested that ascending vagal signals modulate abnormal cortical excitability via various pathways, the precise mechanism of action has not been fully clarified.

Brain stimulation has been attempted for various targets, including the cerebellum, subthalamic nucleus, caudate nucleus, centromedian nucleus, anterior nucleus of the thalamus, hippocampus, white matter tracts, and seizure foci. Responsive neurostimulation (RNS) is already approved in the United States. In the RNS system pivotal trial, patients with intractable partial onset seizures from one or two foci were implanted with neurostimulators, and 1 month later were randomly assigned to receive either active or sham stimulation (1:1). After the fifth postimplant months, all subjects received responsive stimulation in an open-label period (OLP) for a total of 2 years of follow-up after implant placement. The percent change in seizure frequency at the end of the blinded period was −37.9% in the active and −17.3% in the sham stimulation group ($p = 0.012$, generalized estimating equations). The median percent reduction in seizures during the OLP was 44% at 1 year and 53% at 2 years, which represents a progressive and significant improvement over time ($p < 0.0001$).[31] Further investigation to clarify the ideal indications and optimal stimulus parameters is necessary.

The anterior nucleus of the thalamus has been studied in a large RCT called the electrical Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial.[32] One hundred and ten patients with intractable focal seizures were randomly assigned to receive either 5 V of stimulation or none. In the last month of the blinded phase, the treatment group had a 29% greater reduction in seizures compared with a 14.5% reduction in the control group. In the unblinded phase, 2 years after implant placement, patients exhibited a median 56% reduction in seizure frequency; 54% of patients had a seizure reduction of at least 50%. The long-term results of the SANTE trial were recently reported.[33] During the follow-up period, medication and stimulation parameters were changed at the discretion of the treating investigators. The median percent seizure reduction from baseline was 41% at 1 year and 69% at 5 years. The proportion of patients with greater than 50% reduction in seizure frequency was 43% at 1 year and 68% at 5 years, and 16% of patients were seizure-free for at least 6 months. There were no reported unanticipated device effects or symptomatic intracranial hemorrhages. Neuropsychological testing revealed statistically significant improvements in attention, executive function, anxiety, depression, and cognition.

Postoperative Management

I. Postsurgical rehabilitation

Thorbecke et al.[34] reported the effectiveness of an inpatient rehabilitation program following epilepsy surgery. The program included medical monitoring, epilepsy nurse counseling, sports therapy, neuropsychological interview and counseling, psychological counseling, social work support, occupational therapy, and postsurgical education for epilepsy. Patients who participated in the program were three times

more likely than controls to be employed 2 years after surgery. The most significant factor affecting employment after surgery was employment before surgery. Personality disorder was negatively associated with obtaining gainful employment.

II. Postoperative AED management

The AED discontinuation is associated with seizure recurrence in one in three patients rendered seizure-free by epilepsy surgery, and more than 90% of adult patients with seizure recurrence regained seizure control with reinstitution of previous AED therapy.[35] The question of whether and how to maintain or reduce medication after successful epilepsy surgery is still a very delicate and difficult one on which no clear-cut recommendations have been made. The preferences and needs of each patient, especially with regard to activities such as driving and employment, should be seriously considered. Yardi et al.[36] reviewed patients who had undergone TLE surgery and concluded that AED withdrawal increases the short-term risk of breakthrough seizures after TLE surgery and may alter the long-term disease course in some patients.

Conclusion

More than 60 years ago, Penfield and Flanigin[37] analyzed 68 patients with TLE who underwent temporal surgery and were followed over a 10-year period. In 55% of these patients, the outcome was considered successful by both patient and surgeon. About half of these patients with successful outcomes had no seizures following the operation, while the other half had two or three seizures each before the apparent cessation of seizures. Although nowadays we have much greater insight into the inner workings of the epileptic brain through many new modalities such as high-resolution MRI, magnetoencephalography, and broadband analysis of intracranial EEG, the long-term seizure outcome of TLE has remained similar. It is generally considered that complete resection of the "epileptogenic zone" is important for seizure relief. The resection of larger areas may improve seizure outcome in some patients, but the situation is not so always simple. For example, we still do not know why some patients with MTLE with HS become seizure-free after surgery while others with similar clinical characteristics continue to have seizures after surgery. Future breakthroughs in diagnostic and therapeutic procedures are expected to resolve many of the remaining questions.

Comprehensive patient care is very important in the treatment of epilepsy, including surgical therapy. While stopping seizures is the primary goal of treatment, this achievement alone is not enough. To improve quality of life after surgery, comprehensive presurgical evaluation taking psychosocial issues into consideration and postoperative care such as counseling and employment support are necessary (Fig. 5).

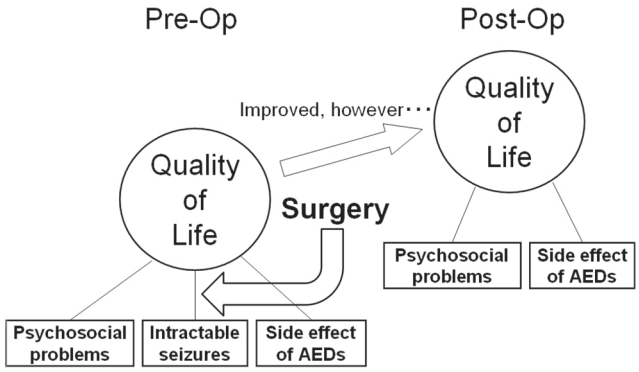

Fig. 5 Diagrammatic representation of the importance of comprehensive care. Intractable seizures may be relieved by epilepsy surgery; however, other problems including psychosocial ones may continue to negatively influence the quality of life. AED: antiepileptic drug.

Conflicts of Interest Disclosure

The author declares that there is no conflict of interest (COI) to disclose regarding this article to the criteria of The Japan Neurological Society.

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Address reprint requests to: Naotaka Usui, MD, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama 886, Aoi-ku, Shizuoka 420-8688 Japan.
e-mail: n-usui@shizuokamind.org