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The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia

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Summary

Objective—Epilepsy surgery is the most effective treatment for select patients with drug-resistant epilepsy. In this article, we aim to provide an accurate understanding of the current epidemiologic characteristics of this intervention, as this knowledge is critical for guiding educational, academic, and resource priorities.

Methods—We profile the practice of epilepsy surgery between 1991 and 2011 in nine major epilepsy surgery centers in the United States, Germany, and Australia. Clinical, imaging, surgical, and histopathologic data were derived from the surgical databases at various centers.

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Supporting Information
Additional Supporting Information may be found in the online version of this article:

Results—Although five of the centers performed their highest number of surgeries for mesial temporal sclerosis (MTS) in 1991, and three had their highest number of MTS surgeries in 2001, only one center achieved its peak number of MTS surgeries in 2011. The most productive year for MTS surgeries varied then by center; overall, the nine centers surveyed performed 48% (95% confidence interval [CI] −27.3% to −67.4%) fewer such surgeries in 2011 compared to either 1991 or 2001, whichever was higher. There was a parallel increase in the performance of surgery for nonlesional epilepsy. Further analysis of 5/9 centers showed a yearly increase of 0.6 ± 0.07% in the performance of invasive electroencephalography (EEG) without subsequent resections. Overall, although MTS was the main surgical substrate in 1991 and 2001 (proportion of total surgeries in study centers ranging from 33.3% to 70.2%); it occupied only 33.6% of all resections in 2011 in the context of an overall stable total surgical volume.

Significance—These findings highlight the major aspects of the evolution of epilepsy surgery across the past two decades in a sample of well-established epilepsy surgery centers, and the critical current challenges of this treatment option in addressing complex epilepsy cases requiring detailed evaluations. Possible causes and implications of these findings are discussed.

Keywords

Epilepsy surgery; Mesial temporal sclerosis; Neocortical epilepsy; Invasive EEG

Mesial temporal lobe epilepsy (m-TLE) has traditionally been equated with the prototype of drug-resistant focal epilepsy. When a randomized clinical trial compared surgical to medical therapy for drug-resistant seizures, patients with TLE were the chosen study subjects.[1] Major epilepsy advocacy groups declare TLE as the most common form of localization-related epilepsy.[2] The bulk of epilepsy research funding focuses around TLE in general, and m-TLE in particular.[3] Against this landscape dominated by a *perception* of TLE as the central driver of the drug-resistant epilepsy burden, multiple recent anecdotal reports and informal surveys[4–6] have implied a decline in the practice of resective surgery in the context of TLE. Therefore, an accurate assessment of “perception” versus “reality” becomes critical for multiple reasons ranging from prioritization of resource allocation to developing patient management strategies.

The current mechanisms of formal large-scale data assessments for epilepsy surgery practices and volumes are limited. In the United States, the often-used Nationwide Inpatient Sample does not distinguish between temporal and extratemporal resections, so differentiating practice patterns between the two surgery types is impossible.[7] Self-reported data from the National Association of Epilepsy Centers are challenging given variation both in the type of centers included and the nature of information collected over time, as this valuable database was designed for administrative goals rather than as a rigorous scientific research tool.[8,9] We present here a large-scale, comprehensive, and systematic survey assessing epilepsy surgery practices across the last two decades at major epilepsy centers in the United States, Europe, and Australia. The survey was intended to provide a valid and objective measurement of the *current* state of epilepsy surgery to guide future practice and research priorities.

Methods

Patient population

Ten individual comprehensive epilepsy centers with a long tradition in epilepsy surgery participated in this survey. These included Cleveland Clinic, Mayo Clinic – Rochester, New York University, Thomas Jefferson University/Graduate Hospital, Yale University, University of Alabama – Birmingham, and University of California Los Angeles from the United States; University of Bonn from Germany; and Austin Health & Royal Melbourne Hospital, The University of Melbourne from Australia. Data from the latter two University of Melbourne centers were combined into one "Melbourne Centre," making a total of nine participating epilepsy centers. These centers were selected because they have well-established comprehensive epilepsy surgery programs, with international reputations, and maintain accurate prospective patient records on their epilepsy surgeries. Centers reviewed their epilepsy surgery research databases for clinical, surgical, and imaging patient characteristics for three milestone years (1991, 2001, and 2011). Only patients 12 years or older were included. Data collected included age at surgery, gender, magnetic resonance imaging (MRI) findings, histopathologic results, and the number and type of epilepsy surgeries. Centers performed en bloc resections of the hippocampus throughout the duration of the study. Overall, data collection was complete in all the surgical databases except for Center 6, which did not collect information on histopathology.

Study variable definitions

MRI and histopathologic findings were classified as showing evidence of mesial temporal sclerosis (MTS) versus not; clear other pathologies such as tumors, cortical malformations, or not; any abnormalities versus completely normal. The types of surgery were categorized into anteromedial temporal resections for m-TLE, neocortical temporal lobe resection, temporal lobectomy-not specified (anterior temporal lobe resection [ATL]), amygdalo-hippocampectomy, extratemporal resections, hemispherectomy, corpus callosotomy, subpial transection, multilobar resections, and invasive EEG evaluations without a subsequent resection.

Statistical methods

Variables of interest including total numbers of all surgeries and total numbers of ATL and proportions of m-TLE-related surgeries were described for 1991, 2001, and 2011. Comparison of the change in total and MTS-related surgeries were performed using paired *t*-tests. In addition to the three milestone dates, six study centers provided complete study data for annual or bi-annual intervals spanning the study period (1991–2011), facilitating more detailed trend analyses. These comprised Cleveland Clinic, Mayo Clinic, NYU, Thomas Jefferson University, Yale, and Melbourne. Using this more detailed dataset, we performed multivariate Poisson regression for MTS rates adjusting for center. The exposure for this model was set as the total number of surgeries per center per year. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX, U.S.A.).

Results

The nine study centers contributed 1,346 patients (mean 149 patients/center; standard deviation of 77 patients; median 114 patients/center). Table 1 illustrates the main staffing changes observed in the study centers between 1991 and 2011. In Figure 1, the variation in the total number of epilepsy surgeries across the three milestone dates (A) is further detailed into the variation in the total number of MTS-related surgeries (C) and the variation in the number of surgery patients with nonlesional epilepsy (E). Overall, Figure 1 suggests a reduction in the number of MTS-related surgeries between 1991 and 2011, and an increase in the number of nonlesional surgical patients. In fact, when the practice of MTS-related surgery was considered in detail (Fig. 2), five of the centers performed their highest number of surgeries for mesial temporal sclerosis (MTS) in 1991, three had their highest number of MTS surgeries in 2001, and only one center achieved its peak number of MTS surgeries in 2011. Although the most productive year for MTS surgeries varied then by center, overall, the nine centers surveyed performed 48% (95% confidence interval [CI] −27.3% to −67.4%) fewer such surgeries in 2011 compared to either 1991 or 2001, whichever was higher. There was a corresponding trend toward reduction in total number of epilepsy surgeries in 2011 compared to the peak value, but this was less than the reduction in MTS surgeries (mean change from peak year = −25.2%, 95% CI −49.2 to +1.0%, $p = 0.1$) The Poisson regression demonstrated a significant reduction in the annual number of MTS cases per center over time (decline of 0.58 cases/year; $p < 0.001$; Fig. 3). In addition, over the same time interval in centers 1–5 (implant without resection data were unavailable from center 6), the proportion of patients undergoing intracranial EEG implantation without subsequent resection increased 3.3 fold: when adjusted for center, the increase was 0.7%/year, $p < 0.001$ (Fig. S1).

In summary (Figs. 1–3), although MTS was the main surgical substrate in 1991 and 2001 (proportion of total resections was $42.6 \pm 22.8\%$ and $36.5 \pm 12.4\%$, respectively), it occupied only $30.5 \pm 10.7\%$ of all resections in 2011. Correspondingly, the mean proportion of nonlesional cases increased from $22.0 \pm 11.2\%$ in 1991 to $33.1 \pm 22.2\%$ in 2011.

Discussion

The international effort presented here provides a longitudinal description of the evolution of epilepsy surgery practices across the last two decades in nine selected major surgical epilepsy centers across the United States, Germany, and Australia. Three main "evolutionary processes" defining the current face of epilepsy surgery can be hypothesized:

1. The practice of m-TLE surgery is decreasing in major surgical epilepsy centers:

Potential explanations are the following:

a. The practice of m-TLE-related surgery is actually not decreasing: this is a purely artificial finding due to an increasing number of extratemporal surgeries leading to a relative drop in the proportion of all surgeries attributed to m-TLE. The gradual concurrent reduction in the *absolute* *numbers* of m-TLE-related surgery (Fig. 1) performed in our centers strongly argues against this possibility and favors a true drop in practice. In fact, this drop in absolute numbers is even more striking, considering that it progressively decreased over time, even though each one of these surgical centers was becoming more established and gaining in reputation as a referral center.

b. The practice of m-TLE-related surgery is indeed decreasing in major epilepsy centers, but this is merely a reflection of varying referral patterns with "simpler" m-TLE-related surgeries occurring in local hospitals instead. This is a critical hypothesis to entertain given the sample bias in our survey. The cohort reported here represents a select group of likely the most complex epilepsy surgery cases, evaluated in specialized centers, potentially underrepresenting easily recognizable MTS cases operated on locally in private practice groups or smaller academic epilepsy programs. Barriers to care[10,11] and disparities in access to epilepsy surgery[12,13] may restrict the choices of patients with drug-resistant epilepsy or simply direct them to obtain care locally. However, recent data from the Nationwide Inpatient Sample demonstrated a gradual overall national reduction in the practice of epilepsy surgery within the United States, across all hospitals and levels of care.[7] This concerning overall reduction in surgical numbers, the continuing long epilepsy duration and high number of anticonvulsant trials prior to epilepsy surgery[10] emphasize the ever-urgent need for early identification and referral of patients with drug-resistant epilepsy for possible surgical evaluation. However, in our study here we found the same pattern of reduced m-TLE surgery in Bonn and in Australia, countries with different healthcare systems and referral patterns. Such a ubiquitous observation of a reduction in m-TLE–related surgeries suggests that although a redistribution hypothesis is possible, it is unlikely to be the only answer.

c. The last hypothesis is that the practice of m-TLE-related surgery is indeed decreasing because the epidemiology of drug-resistant epilepsy is shifting, and there is now a "smaller pool" of drug-resistant epilepsy patients with hippocampal sclerosis as their epilepsy substrate. Under this assumption, every geographic area's local patients with hippocampal sclerosis represent a prevalent pool that is efficiently surgically treated by local surgical epilepsy center(s), but inefficiently replenished due to various factors, including an insidious course of intractability,[14–16] and better treatment of m-TLE risk factors such as infections and complex febrile seizures with anti-inflammatory medications.[17–19] Additional evidence supporting this hypothesis include recent data demonstrating that in addition to a reduction in numbers of MTS cases receiving surgery, the age at surgery is increasing, suggesting a diminishing supply of younger MTS cases.[17]

2. There is an increase in the practice of extratemporal resections, particularly in the context of surgery for nonlesional epilepsy (Fig. 1E,F): Potential drivers for this include better diagnostic techniques and neuroimaging modalities facilitating localization of the epileptogenic zone extratemporally,[20–22] the improved noninvasive functional assessment tools allowing better risk-adjustment such as diffusion tensor imaging for mapping of visual and motor fibers,[23] and the growing literature about possible favorable seizure freedom outcomes for extratemporal lobe surgery.[24–33] It is interesting to observe that although this general trend was true for the cohort as a whole, it was not observed uniformly across centers (Fig. 1E), reflecting varying comfort levels and opinions about appropriateness of surgery in this challenging patient population that may obtain substantial benefit from early surgery.[32]

3. The use of invasive EEG evaluations that do not lead to subsequent brain resections is increasing (Fig. S1). Multiple potential explanations exist for these findings in 6/9 centers. A growing experience with invasive EEG implantations may have led to safer use of this technology and thus reduced the “implantation threshold,” even in patients with an anticipated suboptimal yield of epilepsy localization. Alternatively, as epileptologists encounter a mounting plethora of imaging and electrophysiologic techniques (ictal SPECT, PET, MEG, EEG-fMRI, etc.), it becomes easier to find “concordance” between any given number of these tests and thus formulate misleading localization hypotheses and subsequent unsuccessful invasive evaluations. Regardless of its causes, this finding highlights a very challenging situation. The decision to proceed directly to a resection versus perform an invasive EEG evaluation to test an epilepsy localization hypothesis versus to withhold surgery altogether is a very complex one: the choice depends on multiple factors, including the epilepsy severity, the risks of any neurological functional deficits with the anticipated brain resection, and the expertise of the surgical center in performing different invasive EEG techniques. Until better nonsurgical treatment options become available, it remains critical to use all noninvasive and invasive tools in our disposal to investigate the possibility of resective surgery. On the other hand, given the significant risk of neurological complications and financial costs associated with such investigations, we need to learn how to better target our presurgical testing and restrict invasive EEG investigations to patients with a testable localization hypothesis.

Limitations

The heterogeneity of our findings is undeniable. Although a variable practice was most obvious in relation to management of nonlesional drug-resistant epilepsy (Fig. 1E,F), there was also demonstrable variation in the extent and rate of drop in the surgical MTS volumes among centers and over time. There are likely multiple factors accounting for this beyond the "availability" of MTS cases, including differences in timing of when individual surgical centers were established, variations in staffing over time within a surgical center, disparities in referral and reimbursement patterns, changes in the type and number of patients evaluated for possible surgery, and evolving pre-surgical diagnostic tools. A newly established center may find a prevalent pool of nonoperated MTS cases, and as it grows will increase its activity. Moreover, the center may choose at any time to extend its reach in the absence of a local pool of surgical patients. This variability in practice and variability in overall presenting patient distribution over time is beyond our capability to quantify on a center by center basis. But the overall trend is undeniable, particularly as it was observed DESPITE an increase in the number of epileptologists and neurosurgeons between 1991 and 2011 in our study centers (Table 1) and suggests that even as a center continues its activity over time, eventually the number of MTS patients will decline. Such an idea is supported by observations already reported in multiple healthcare systems, including on the national level in the United States using the NIS database,[7] in the United Kingdom where the number of children receiving surgery for epilepsy had increased annually up to, and declined after, the establishment of Children's Epilepsy Surgery Service centers,[34] and in Germany where an epidemiological analysis of 2,812 patients who had TLE surgery between 1988 and 2008 showed an early increase in the proportion of patients with MTS during the first few years studied, only to subsequently demonstrate an increase in the age and duration of epilepsy in patients with MTS despite stable overall surgical numbers over time interpreted to suggest a reduction in incidence of MTS.[17]

Implications of findings for future research

While debating the *causes* of our findings is important, it is critical to advance the discussion further and tackle their *implications*. Making this leap is essential to develop the "evolutionary" adaptive steps that would be necessary for the betterment of the care of patients with drug-resistant epilepsy. Regardless of the cause, our data suggest that m-TLE related surgeries no longer account for the major burden of surgical epilepsy in major established epilepsy centers in the developed world, and an increasing number of patients with complex nonlesional epilepsy are being assessed/undergoing surgery. As our patient population is expanding in complexity, so should our clinical care resources and our research priorities. Given our findings, specific suggestions for future research include:

1. Thorough and systematic epidemiological research to better understand and improve the utilization of epilepsy surgery, for ALL potential surgical candidates. Such work will be critical to optimize the reach of epilepsy

surgery for patients in "underserved" pockets with drug-resistant m-TLE, and to enhance the identification of adequate surgical candidates among the challenging group of nonlesional patients with drug-resistant focal epilepsy.

2. Methodologically sound outcomes research to assess the effectiveness of various surgical procedures and presurgical evaluation tools given the observed heterogeneity among centers in their management of patients with nonlesional drug resistant epilepsy. This variation together with the increase in the number of invasive evaluations without subsequent resections highlight a need to improve patient selection, presurgical evaluation protocols, and outcomes of care in this complex surgical population.

3. Expanding the scope of clinical and basic science research studying extra-temporal epilepsy given its growing contribution to the surgical epilepsy burden. Continuing to predominantly focus various stakeholder resources on m-TLE alone will fall short of addressing the present and future needs of surgical epilepsy.

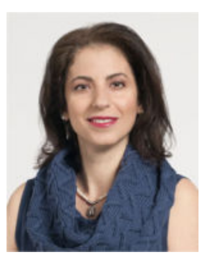
Conclusions

We cannot overemphasize the fact that it remains critical to reach pockets of "underserved" epilepsy population in developed and developing countries with likely high prevalence of hippocampal sclerosis. Understanding/solving the barriers to care remain paramount, including the possibility that patient perception of disease severity and knowledge of treatment options is little understood. In addition, our data suggest that we also owe a significant effort to our patients with drug-resistant nonlesional epilepsy to better understand their disease, localize it, resect it safely, grasp and improve the long-term success of surgery, and even better, prevent the development of epilepsy. This will require major research efforts, but our data suggest that these efforts would seem well-justified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Biography



Dr. Lara Jehi is an adult epileptologist and the director of epilepsy research at Cleveland Clinic.

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Key Points

- The practice of surgery for mesial temporal lobe epilepsy is decreasing in major surgical epilepsy centers
- There is an increase in the practice of extratemporal resections, particularly in the context of surgery for nonlesional epilepsy
- The use of invasive EEG evaluations that do not lead to subsequent brain resections is increasing

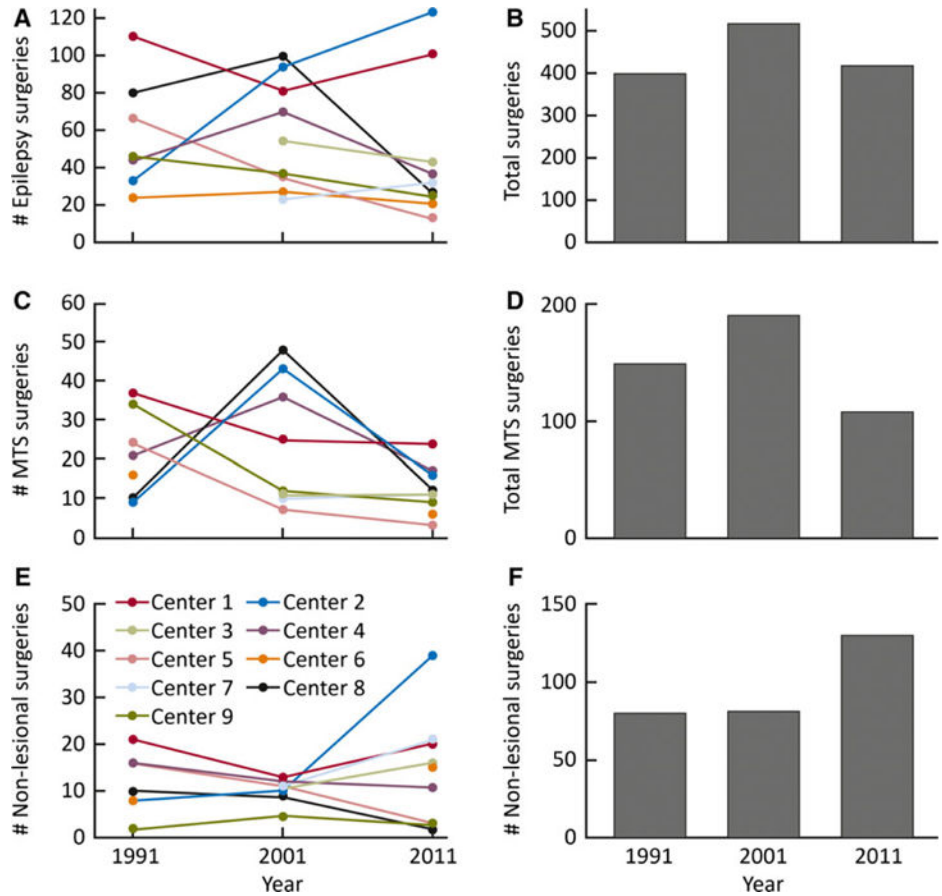

Figure 1.

Number of epilepsy surgeries reported in 1991, 2001, and 2011 for nine epilepsy centers. (**A**) Total epilepsy surgeries at each time point for individual epilepsy centers. Two centers (3 and 7) were not active or did not track statistics in 1991. (**B**) Sum of all epilepsy surgeries across the nine epilepsy centers for each time point. The overall number of epilepsy surgeries at these nine centers does not exhibit consistent trends. Some centers (2, 6, and 7) reported overall increases in total surgeries whereas others reported declines. (**C**) Number of MTS-related surgeries at each time point for individual centers. All but one center (7) reported a decline in MTS-related surgeries in 2011 compared to a prior peak in either 1991 or 2001. (**D**) Sum of all MTS-related surgeries across the nine centers. Overall, there was a decline in total MTS-related resections in the group. (**E**) Number of surgeries performed for nonlesional epilepsy (NL) at each time point for individual centers. Five of the nine centers reported an increase in the number of surgeries performed for NL epilepsy in 2011 compared to prior years. (**F**) Sum of all NL epilepsy–related resections across the nine centers. Overall, there was an increase in the number of NL epilepsy–related surgeries in 2011.

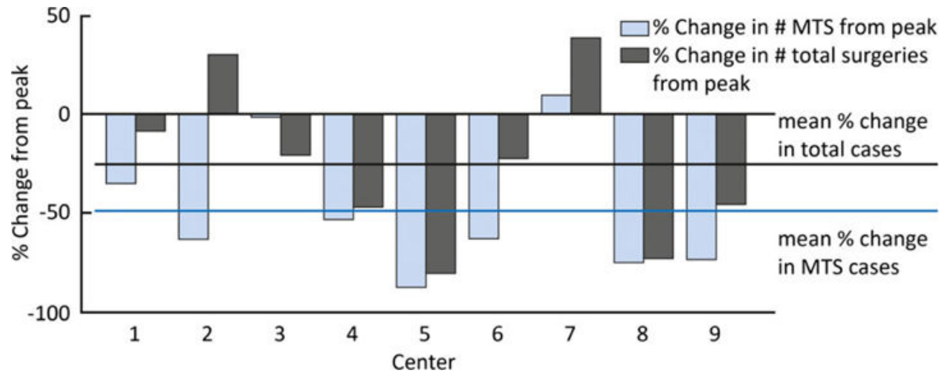

Figure 2.

Plot of the percent change in total and MTS-related surgeries at each center compared to the peak number of surgeries (the highest value reported in the prior two time points, 1991 or 2001). All but one center reported a decline in MTS-related surgeries in 2011 compared to the prior peaks. The mean change was 48.0% (95% CI −27.3 to −67.4%, blue line). Although most centers also reported a decline in epilepsy surgeries overall, this change was less pronounced (mean change −25.6%, 95% CI −51.0 to +1.0%, black line) and two centers reported an overall increase.

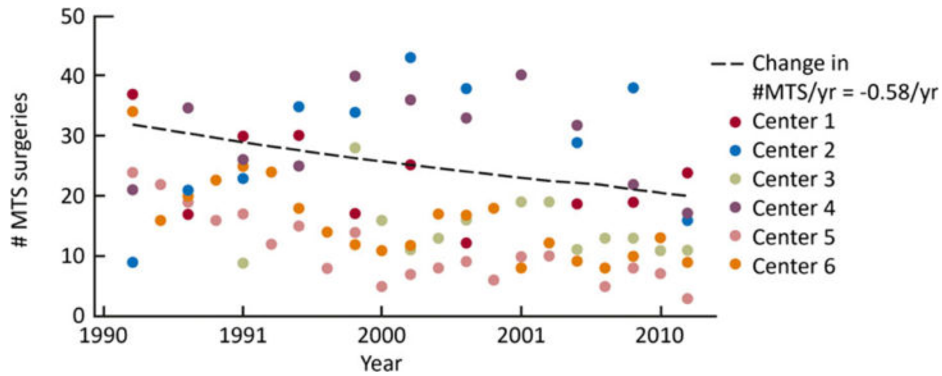

Figure 3.

Number of epilepsy surgeries per year for five centers that provided annual or biannual data from 1991 to 2011. When adjusted for center, there was an overall reduction of 0.34 MTS-related surgeries per year (dashed line) across the two decades. This translates into a 1.3% reduction in MTS-related surgeries annually compared to 1991.

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Table 1

Staffing changes (number of active neurosurgeons and epileptologists) in the participating centers during the study period

	1991		2001		2011	
Center	No. of adult epileptologists	No. of epilepsy neurosurgeons	No. of adult epileptologists	No. of epilepsy neurosurgeons	No. of adult epileptologists	No. of epilepsy neurosurgeons
1	3	3	6	2	6	2
2	5	1	8	1	9	2
3	3	1	8	1	13	1
4	2	1	4	1	5	2
5	4	1	5	1	8	2
6	6	1	6	1	6	1
7	2	2	4	2	4	2
8	3	4	4	4	4	2
9	2	2	7	2	12	5

Major leadership changes occurred in centers 5 and 2 between 2001 and 2011.