Epilepsy surgery near or in eloquent cortex in children--practice patterns and recommendations for minimizing and reporting deficits

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Running title: Recommendations for minimizing and reporting deficits

Key words: Epileptogenic zone, Critical cortex, Epilepsy surgery strategies, Deficit scale

Number of text pages: 11
Number of words (summary): 124
Number of words (main text): 2868
Number of tables: 5
Number of figures: 2 in color

Summary

Objective: We aimed to investigate the current practices guiding surgical resection strategies involving epileptogenic zones (EZ) near or in eloquent cortex (EC) at pediatric epilepsy surgery centers worldwide.

Methods: A survey was conducted amongst 40 pediatric epilepsy surgery centers worldwide on the weight assigned to diagnostic tests used to define the EZ and EC, how EC is viewed, and how surgeries are planned for foci near or in eloquent cortex.

Results: A descriptive analysis was performed that revealed considerable variation in the usages of diagnostic tests and resective strategies towards EZ and EC.

Significance: The wide variation in strategies may contribute to undesirable outcomes characterized by poor seizure control with added deficits, and underscores the need to establish best practices in pediatric epilepsy surgery. The survey data was used to formulate a set of recommendations to help minimize deficits and to report them consistently.

Introduction

Epilepsy surgery is now widely used in the management of children with medically refractory epilepsy; the number of centers worldwide that perform epilepsy surgery in children has risen substantially over the recent years. The ultimate goal of the resective surgery is cure and is achieved through removal or disconnection of the epileptogenic zone (EZ), a task that is particularly challenging in children who have EZs close to or involving eloquent cortex (EC). Recommendations published through the joint efforts of the ILAE Diagnostic Methods Commission and the Pediatric Epilepsy Surgery Task Force[1] helped to standardize the overall evaluation process in specific substrates commonly encountered in children. Nonetheless, significant subjectivity exists in how tests are used to define the EZ and EC, which areas are considered to be "critical" function, notions of plasticity and influence of age, and what defines a complete resection of the perceived EZ. While some centers are conservative and favor a smaller albeit "incomplete" resection to preserve eloquent function[2-4], "complete" resections of the EZ are believed to achieve higher rates of seizure freedom and can prompt aggressive resection of EC[5].

Most surgical series report outcomes with respect to seizure control but the deficits incurred are generally not completely documented[6-16], a consideration particularly relevant for the subset of patients in whom the EZ is close to or involves the EC. Table 1 presents the possible outcome categories based on seizure freedom and deficits incurred. Category I, i.e., seizure freedom without any deficit is optimal, Categories II (seizure free with deficit) and III (not seizure free, no deficit) are acceptable, while category IV (not seizure free, with deficit) is the least desirable. Unfortunately, given the uncertainty surrounding defining the EZ in practice, category IV outcomes are not uncommon[2,8,17,18] and presumably have a significant detrimental impact on the quality of life. Some degree of standardization is thus required.

The ILAE Pediatric Epilepsy Surgery Task Force of the ILAE Commission for Surgery and Pediatrics undertook this challenge and conducted a survey of surgical practice

patterns at centers worldwide as a step towards establishing recommendations to guide surgical strategy aimed at minimizing category IV outcomes.

Methods

A survey questionnaire was constructed using Surveymonkey.com. The information collected included when the participating center was established, volume of resective epilepsy surgeries performed annually, and the professional role of the respondent. The survey did not require respondents to query their respective databases and was kept qualitative to promote center participation. Recognizing the limitations of a survey format that only allowed entry for each question individually, several free text comment sections were also included to capture the complex multifactorial considerations that generally enter surgical decision-making.

A total of 38 question categories included 84 individual queries on the EZ, EC, plasticity, and resection strategies. Respondents were asked to assign weights of 1 to 5 to various diagnostic test findings used to define the EZ; a weight of 1 implied that the finding had low usefulness in defining the EZ while a weight of 5 implied resection of this area would be considered "essential" to achieve seizure freedom and might prompt extension of the resection to include EC. The reliability of various tests to define EC was likewise weighted 1 to 5, and this scale was also used to rate how critical various functions were considered and their perceived degree of plasticity across age groups. Queries on surgical strategies assessed resection of EC under specified scenarios including presence of a lesion and its relationship to EC, and consideration of the possibility of using a staged approach with initial conservative resections. Following each set of questions, there was a comment box for participants to provide more detailed input or explanations.

The survey was sent to all 76 members of the Pediatric Epilepsy Surgery Task Force in January 2015. A reminder was sent in March 2015 and the survey was closed on May 31, 2015. No patients were contacted or involved in the survey. The data was quantified and analyzed using the surveymonkey.com analytics tools to define practice patterns. Practice

patterns showing substantial variations along with individual comments were used to draft a set of recommendations. A summary of survey results and recommendations was presented at a special session at the 33rd congress of the ILAE in Istanbul, Turkey in September 2015 and at the American Epilepsy Society meetings in Philadelphia in December 2015 and Houston in December 2016.

Results

There were 40 respondents to the survey, 24 neurologists and 16 neurosurgeons, representing a total of 34 centers. Thirty-two (80%) respondents had been conducting epilepsy surgeries prior to 2000. Most of the respondents were from North America (n=21) and Europe (n=11), with Australia, Asia and South America having three respondents each.

Defining the Epileptogenic Zone

In defining the EZ, the seizure aura was weighted heavily by participants, with 73% scoring it as a 4 or 5, while the early seizure semiology and postictal findings scored lower (63% and 9% respectively) (Table 2). The type of MRI lesion played a significant role in the amount of weight given to the MRI. While focal cortical dysplasia and vascular lesions were heavily weighted along with the MRI findings of hemimegalencephaly and Rasmussen's encephalitis, weights assigned to other types of lesions including polymicrogyria showed considerable variation across centers. With regards to nuclear medicine imaging, 35% of respondents weighted ictal SPECT hyperperfusion and PET hypometabolism heavily in favor of extending the resection to EC, with 50% considering SISCOM and PET hypermetabolism reliable. This percentage was 75% for MEG/ESI clusters, a rating that was even higher than for interictal epileptiform discharges recorded on intracranial EEG.

The different types of focal background abnormalities seen on intraoperative electrocorticography (ECoG) were weighted variably; continuous epileptiform discharges

were regarded as a reliable marker of the EZ by 90% of the respondents. Regarding extraoperative recordings, the ictal onset zone on the intracranial EEG was seen as the most reliable marker of the EZ by all respondents but early seizure propagation and specific patterns such as high frequency oscillations and ictal DC shifts were variably weighted.

Defining Eloquent Cortex

Electrical stimulation mapping (ESM) was regarded as a reliable modality to define eloquent cortex by 90% of the respondents; fMRI and MEG were also felt to be reliable by 75% of the respondents whereas TMS was lower at 45%. Centers were asked to grade how "critical" they viewed specific functions. Broca and Wernicke areas were regarded as highly critical by all respondents (Figure 1).

Verbal memory and the dominant hand motor function were likewise regarded highly critical by over 90% respondents. The non-dominant hand (83%) came in next followed by leg motor at 66% and homonymous visual fields with 63%. Motor face, executive function, non-verbal memory, and calculation were regarded critical by fewer than 50% of respondents. With regards to plasticity of language cortex, 85% of the respondents considered it to be maximum below age 5 years, whereas 15% considered maximum plasticity to extend to the end of the first decade.

Surgical Strategies

There was a wide range in the threshold of the chance of seizure freedom based on the pre-operative assessment that would be required to accept post-operative deficits. Thirty percent of the respondents considered that the possibility of seizure freedom would have to exceed 90% in order to accept post-operative deficits, while the majority accepted a moderate chance (60-80%) chance of seizure freedom and 10% of respondents were comfortable accepting deficits at estimated rates of seizure freedom as low as 50%. Eighty five percent of respondents adopted a conservative strategy favoring an initial EC-sparing resection, whereas the remaining generally opted for more aggressive "complete" resections at initial surgery. Involvement of EC by an MRI lesion likely prompted its

resection by nearly 30% of respondents whereas only 12% of respondents would consider resection of EC in non-lesional cases. In patients where the MRI lesion was nearby but did not involve EC, 25% would extend the resection to include EC based solely on functional abnormalities ; the remaining would opt for lesionectomy alone.

With respect to mesial temporal resections, in patients with proven unilateral temporal lobe onsets and with preserved verbal memory function, 40% would resect the hippocampus only if there was evidence of sclerosis on MRI scans, 30% would resect it in any case, 20% would tailor using invasive EEG, whereas only 10% would refrain from pursuing surgery.

Protective strategies such as intraoperative functional mapping including motor mapping under anesthesia were employed by 90% of respondents, and awake surgery required for language mapping was used by 65% when feasible (Table 3). Fifty percent of respondents also performed subcortical tract mapping, multiple subpial transections were performed by 30%. With regard to specific etiologies, respondents were more inclined to resect EC if the substrate was focal cortical dysplasia versus all other substrates (85% vs 60%).

Discussion

The survey responses and comments reflect different practice patterns and help explain the biases that influence surgical strategies towards resection of EC across centers. The survey participants represent a majority of the main epilepsy surgery centers worldwide. The survey results show that amongst these centers, there is a considerable amount of variability in how the EZ and EC are delineated. Furthermore, there does not appear to be a set of standard circumstances that are agreed upon to justify resection of EC. These results raise grave concern that a lack of uniform strategy contributes to unacceptably high levels of category 4 outcomes. We recognize that a survey requiring entries for individual queries may not reflect the complexity of the analyses that go into surgical decision making. Besides the results of clinical tests, factors such as seizure burden, patient age, or coexisting encephalopathy also play a role; family preference or palliative

goals are also important factors in the complex-decision making process in epilepsy surgery. Furthermore, there will always be exceptional cases that require deviation from pre-established practice. However, we feel that in the more normative or routine cases and given the lack of class I or II evidence to guide practice, recommendations derived from expert opinion help standardize surgical strategies in pediatrics (Table 4)

The survey did not specifically question the technologies available at each center and how often they were used but local biases and subjectivity of defining the EZ may explain the widely varying assigned weights to several diagnostic test findings in the survey. For example, clusters of interictal spike sources on MSI or ESI may be falsely localizing but were rated highly as were PET hypometabolism or ictal SPECT hyperperfusion that may be more or less extensive than the EZ. Likewise, ictal semiology or postictal findings can represent the symptomatogenic zone rather than the epileptogenic zone. Awareness of the limitations of individual tests in defining the EZ may help minimize bias[1]. Although it was not directly questioned in the survey, participants' comments indicated that pre-existing clinical deficits generally prompt more aggressive resections. However, it should be recognized that it may not always be feasible to differentiate fixed deficits from those resulting from an epileptic encephalopathy.

The minimum amount of tissue that requires removal is generally surmised based on Bayesian analyses of all data available. Unfortunately, however, our ability to accurately predict seizure-free outcomes is limited and while completeness of the perceived EZ resection is well documented to correlate with successful outcome, there remains substantial ambiguity as to how it is defined. Within the context of discrete MRI lesions, a lesionectomy generally achieves seizure freedom in the majority of patients[19]; the use of neuronavigation or intraoperative MRI helps identify residual lesions that can be resected[20]. Extending the resection to include EC revealing functional abnormality i.e., a "complete" resection, purportedly increases the rates of seizure freedom[21-26], but a substantial proportion continue to have seizures[27]. Thus, one could argue against resecting EC uninvolved in a discrete anatomic lesion on the basis of functional

abnormalities alone and in favor of adopting a staged strategy with an initial conservative EC-sparing resection in MRI lesional cases; an approach adopted by an overwhelming majority of respondents. One consideration to this strategy would be the age of the patient as the level of plasticity may influence the decision to resect near critical cortex, especially with Broca or Wernicke's areas. Placement of responsive neurostimulation implants may be considered when resection is not an option. The staged approach however requires due consideration of the possibility of precipitating status epilepticus following incomplete resections[28], the added costs, the potential risk of re-operation should seizures persist[29], and the potential reduction of plasticity with increasing age.

There was general agreement that the etiologic substrate played a significant role in the decision to extend the resection to EC if necessary[30]. Amongst hemispheric syndromes, while Rasmussen's encephalitis or hemimegalencephaly require hemispherectomy, the EZ in hemispheric polymicrogyria is often more restricted and seizure freedom can be achieved without EC resection in a subset of children. Vascular lesions and discrete tumors are generally treated without including surrounding EC whereas FCD lesions appear to be the strongest justification for extending resections to include functional abnormalities involving EC. Unfortunately however, this etiologic substrate has one of the lowest rates of seizure freedom following complete resections[22] and is thus most likely to experience class IV outcomes up to rates approaching 50%[2,8,17,18]. For type IIb dysplasia, complete cortical resection (but not necessarily resection of the subcortical transmantle tail) appears to be required for seizure freedom[31].

Current views of how critical the various functions of EC displayed some variation. While there was near unanimous agreement that language, dominant hand motor function, and memory were critical, the perceived importance of leg motor, non-dominant hand, visual fields and other functions was much more variable, with a substantial proportion of respondents regarded these as relatively reasonable to sacrifice. Specifically with regards to mesial temporal resections with preserved memory function, the majority would consider resection only in the presence of mesial temporal sclerosis on MRI. Resection strategies were further compounded by uncertainties surrounding plasticity and

impact of deficit on quality of life across different age groups. It was generally agreed that face motor function recovers almost completely following resection. With regards to language cortex, while most respondents accept age 5 years as the upper limit beyond which plasticity starts to decline, a minority believed that full plasticity extended to the end of the first decade; a presumption that prompts resection strategies carrying risk of incurring long-term deficits. Irrespective of one's biases towards the handling of EC, wider usage of protective strategies such as awake surgery when feasible, tractography and intraoperative navigation tools, and intraoperative functional mapping is justified and strongly recommended[3,20,32,33,34,35]. There is also increasing emphasis on ensuring the integrity of white matter tracts via subcortical mapping to maximize preservation of eloquent function[36] and deployment of minimally invasive surgical strategies[37].

The respondents varied considerably in their expectation of the chances of seizure freedom that were considered acceptable thresholds to "justify" a new deficit ranging from 50% to exceeding 90% This is of considerable concern since lowering the acceptable threshold for expected seizure freedom increases the chance of a category IV outcome. However, there was virtually unanimous agreement that surgical decisions towards EC resection should be made in conjunction with the family. This is worthy of further dialogue. While most parents and caregivers are aware of the seizure burden and are rightfully concerned in alleviating it, they are generally less aware of the consequences of new deficits and their potential impact on quality of life. Bias in how this information is presented to the family may thus significantly influence their willingness to accept a new deficit for their child. Better attempts to explicitly explain deficits including video clips of subjects who have undergone EC resection are used by some centers and should be considered as a standard protocol in counseling families faced with this difficult decision.

Whereas seizure freedom following surgery is reported uniformly, reporting of other outcomes including the occurrence of planned deficits is variable. Whereas some studies use specific tools to document deficits[38], most epilepsy surgical outcome series do not document the type or severity of new deficits incurred. Sometimes deficits are reported

under the broader category of complications or unplanned deficits and it not possible to sort out those that were a part of planned surgical strategy[39]. The majority of respondents perform neuropsychological testing post-operatively, yet there is little reporting on cognitive outcomes, neurodevelopment and the long term impact of surgery on quality of life. We recommend the deficit index scale proposed in Table 5 to standardize reporting of both planned and unplanned deficits. Such data reporting is the first step towards measuring impact on quality of life at various ages and the development of more objective decision analysis algorithms balancing the tradeoff between seizure freedom and acceptable deficits[40].

Conclusions

The survey demonstrates that there is variation among the major epilepsy surgery centers in the process of defining the EZ and EC, acceptable outcomes, and the use of protective strategies. Our recommendations include using the full spectrum of tools to educate families on all potential functional losses that may result from a proposed resection as what is deemed "critical" by practitioners is not consistent amongst centers. Multimodal mapping should be implemented to ensure that maximum EC is spared while removing the EZ. Staged surgeries with function-sparing resections should be considered when the perceived EZ involves EC, especially in MRI-negative cases. Finally, standardized reporting of deficits using the recommended classification will facilitate shifting the focus of surgical outcomes to overall wellbeing of the patient from both a seizure and functional perspective.

Key points:

- The results of a survey reflecting current practices guiding surgical resection strategies involving epileptogenic zones near or in eloquent cortex at pediatric epilepsy surgery centers worldwide are presented.

- The survey data was used to formulate a set of recommendations to help minimize deficits
- A scale to report deficits consistently is proposed.

Acknowledgements: We wish to thank the International League Against Epilepsy (ILAE) and for its support of the pediatric epilepsy surgery task force.

Disclosure of Conflict of Interest: This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent official policy or position of the ILAE.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
None of the authors has any conflict of interest to disclose.

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Figure legends

Figure 1. Weights of how “critical” various functions were considered: Response percentages

Table 1: Categories of outcome following resective surgery

	No Deficits	Deficits
Seizure free	I	II
Seizures persist	III	IV

Table 2: Response percentages of weights assigned to findings defining the epileptogenic zone

Semiology	**1**	**2**	**3**	**4**	**5**	**N/A**
Aura suggestive of critical cortex involvement	0.0	3.0	24.2	45.5	27.3	0.0
Clinical focality early in the seizure	0.0	12.1	24.2	33.4	30.3	0.0
Post ictal sustained focal deficit	21.2	30.3	39.4	9.1	0.0	0.0
MRI Lesions	**1**	**2**	**3**	**4**	**5**	**N/A**
All lesions	3.1	0.0	28.1	50.0	15.6	3.2
Focal Cortical Dysplasias	0.0	0.0	9.1	24.2	66.7	0.0
Vascular lesions	0.0	0.0	25.0	18.8	56.2	0.0
Sturge Webber Syndrome	0.0	3.1	9.4	21.9	62.5	3.1
Polymicrogyria	3.1	9.4	34.4	28.1	25.0	0.0
Hemimegalencephaly	0.0	6.3	3.1	3.1	84.4	3.1
Rasmussen's Encephalitis	0.0	3.1	3.1	6.3	84.4	3.1
Hypothalamic hamartoma	6.5	3.2	6.5	25.8	51.6	6.4

Encephalomalacia/ Infarct	6.5	9.7	22.6	25.8	32.2	3.2
Nuclear Medicine	**1**	**2**	**3**	**4**	**5**	**N/A**
SPECT Ictal Hyperpefusion	9.4	9.4	37.5	21.9	9.4	12.4
SPECT Interictal Hypoperfusion	25.0	40.6	21.9	0.0	0.0	12.5
SPECT Subtraction-SISCOM	6.1	3.0	24.2	30.3	18.2	18.2
PET Focal Hypometabolism	12.5	9.4	37.5	31.3	6.2	3.1
PET Focal Hypermetabolism	12.9	9.7	19.3	29.0	19.4	9.7
MEG	**1**	**2**	**3**	**4**	**5**	**N/A**
Interictal Spike Clusters	3.1	3.1	9.4	37.5	9.4	37.5
Ictal Onset Discharges	0.0	9.4	3.1	18.8	25.0	43.7
Ecog	**1**	**2**	**3**	**4**	**5**	**N/A**
Focal Attenuation of Background	12.9	19.3	25.8	16.1	6.5	19.4

Focal Burst Suppression	6.1	9.1	21.2	30.3	15.1	18.2
Epileptiform Discharges	6.1	12.1	36.4	15.1	12.1	18.2
Continuous Ictal/Interictal Discharges	3.0	6.1	0.0	24.2	48.5	18.2
High Frequency Oscillation	3.1	6.3	9.4	18.8	15.6	46.8
Extraoperative invasive	**1**	**2**	**3**	**4**	**5**	**N/A**
Ictal Onset Zone	0.0	0.0	0.0	18.2	78.8	3.0
Early Propagation	0.0	12.5	15.6	43.8	25.0	3.1
High Frequency Oscillation	3.2	3.2	19.3	19.4	22.6	32.3
Ictal DC Shift	12.5	3.1	12.5	21.9	9.4	40.6

Table 3: Protective Strategies Employed by Respondents

	Percentage of Responses	
	Yes	No
Awake surgery for language mapping when feasible	67	33
Intraoperative mapping	94	6
Sub-cortical tract mapping	55	45
Multiple Subpial Resections	33	67

Table 4: Recommendations to minimize deficits

1) Better understanding of the limitations of all data used to define the EZ: no single diagnostic test finding is a definitive marker for the EZ and therefore, resection of the hypothetical EZ region does not always ensure seizure freedom. All functional tests are additionally prone to potential false localization or can overestimate the size of the EZ.
2) Counseling of families with better tools to document impact of proposed deficits.
3) Staged surgery with initial function-sparing resection should become the preferred strategy, especially in MRI-negative cases or where the MRI lesion is near EC.
4) Wider usage of multimodal mapping and "protective" surgical strategies such as intraoperative functional mapping.

Table 5. Classification to report planned or unplanned deficits

Class	Deficit type
A	None
B	Any deficit lasting < 3 months, or permanent motor face, somatosensory, executive function, upper quadrant visual field
C	Permanent leg/non-dominant hand, non-verbal memory, lower quadrant or full visual field,
D	Permanent language, dominant hand, verbal memory