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Review

Current challenges in the practice of epilepsy surgery☆

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ABSTRACT

The accurate prediction of individual outcomes after epilepsy surgery represents a key challenge facing clinicians. It requires a precise understanding of surgical candidacy and the optimal timing of surgery to maximize a range of outcomes, including medical, psychosocial, cognitive, and psychiatric outcomes. We promote careful consideration of how epilepsy has affected an individual's developmental trajectory as key to constructing more differentiated profiles of postsurgical risk or resilience across multiple outcome measures. This life span approach conceives surgery as a crucial "turning point" in an individual's development from which varied outcome trajectories may follow. This helps clinicians understand the expectations patients and families bring to surgery, and emphasizes the interplay of factors that determine a patient's outcome. It also promotes comprehensive, longitudinal assessment of outcome using data analytical techniques that capture individual differences and identify subgroups with similar trajectories. An ongoing challenge facing clinicians is the development of an outcome classification system that incorporates outcomes other than seizures. We illustrate two emerging areas of research shaping how we define surgical candidacy and predict outcome: (1) using cortico-cortical evoked potentials to identify pathways of seizure propagation and cortico-cortical networks mediating cortical functions, and (2) predicting postoperative depression using a model that incorporates psychosocial and neurobiological factors. The latter research points to the importance of routine follow-up and postoperative psychosocial rehabilitation, particularly in patients deemed at "high risk" for poor outcomes so that early treatment interventions can be implemented. Significantly more research is needed to characterize those patients with poor outcomes who may require re-surgery.

1. Introduction

Of all its lessons, the history of epilepsy surgery teaches us most about the challenges and pitfalls of accurately predicting the individual outcomes of our patients after surgery. Advances in technology, first encompassing the era of electroencephalography and then neuroimaging, have without doubt increased our capability for accurately localizing the seizure focus [1]. These advances, however, have brought their own challenges, with increasing sophistication of our approach promoting the use of surgery in patients with more difficult-to-localize seizures. It is also the case that patient outcomes occur within the broader context of each individual's life history, and that this history may bring psychological and social complexity to the epilepsy surgery setting. Our challenge as we move forward is to improve our ability to systematically account for the complex interplay of factors that occurs in each individual as we endeavor to identify "suitable" surgery candidates, and then predict and assess the clinical outcomes of these individuals. In this respect, ongoing development of clinical skills in both the medical and psychosocial domains of epilepsy surgery is essential.

2. The modern-day practice of epilepsy surgery

It is generally accepted that the goal of epilepsy surgery is to treat or manage intractable seizures by maximizing seizure relief, minimizing adverse effects, and improving patient "quality of life" [2]. Prerequisites for consideration of surgery typically include proven intractability to conventional antiepileptic drugs, identification of the site of the epileptogenic region and ideally a causative lesion, documentation of possible neurological or cognitive deficits resulting from proposed procedures, evaluation of the psychosocial and psychiatric status of the patient, and consent for the surgical intervention and medicosocial treatment thereafter [3].

The undertaking of epilepsy surgery invokes a series of processes, each of which requires careful consideration, as they give rise to some

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of the key challenges in the modern day practice of epilepsy surgery. These processes include: (1) determination of surgical candidacy and the timing (medical and personal) of surgery based on the completion of a comprehensive presurgical evaluation; (2) consideration of the most appropriate surgical method and approach; (3) preparation for the provision of postsurgical treatment including rehabilitation; (4) comprehensive evaluation of outcome; and (5) in some patients, consideration for re-surgery. Management of these processes is crucial to ensure that the surgical program progresses smoothly for each patient. The program starts when there is medical intractability and should include all medical and psychosocial interventions from the beginning. This means that the surgery program requires an interdisciplinary approach for the provision of comprehensive management and care [4].

3. Current challenges in the practice of epilepsy surgery

3.1. The challenge of more precisely defining "surgical candidacy"

Ideally, consideration of surgical candidacy should be based on the findings of a comprehensive presurgical evaluation that includes seizure diagnosis; neurophysiological, neuroimaging, and neurocognitive investigations, and psychiatric and psychosocial assessments, as well as counseling to address expectations of surgical outcome and the requirements of postoperative rehabilitation [5,6]. Each aspect of this evaluation may pose challenges for the treating surgical team, as it necessitates a breadth of technological and clinical expertise, as well as team cohesion to reach a consensus about the weight assigned to specific findings and the net result for a given patient. Considerable variability currently exists across centers in the type of presurgical investigations routinely undertaken to determine surgical candidacy. This is evident, for example, in the use of invasive presurgical techniques, such as intracranial EEG recordings and the Wada test to precisely delineate zones to be resected and spared, although there is an increasing trend to use less invasive functional imaging techniques where possible [5,7,8]. Variability in routine presurgical investigations across centers poses a significant challenge for interpreting the outcomes of studies as the influence of this variability has not been systematically addressed in research to date. Similarly, the presurgical evaluation informs the most suitable surgical methods and approach to be employed, with variability in surgical techniques across centers leading to increased reports of pathology- and resection-specific outcomes [9].

Even more fundamental to these issues are the differing levels of stringency used to define "medical intractability" across studies [10], with adequate trials of at least two antiepileptic drugs (AEDs) now serving a minimum requirement [11]. However, if our aim is to perform a more precise risk–benefit analysis of surgery versus medical treatment for a given patient, we still require greater understanding of the natural history of epilepsy and its treatment. This is best derived from community-based outcome studies that follow individuals over the long term, which are currently lacking in the literature [12]. As noted by Langfitt and Wiebe, the risk–benefit balance "differs across syndromes, patients, and within patients over time" [10]. The key clinical challenge is to improve our ability to identify those patients whose seizures will ultimately prove to be intractable versus those whose seizures will be controlled on medical treatment, thereby precluding the need for surgery in some patients while optimizing the timing of surgery for others.

For those patients deemed to have intractable seizures, also fundamental is the need to define the purpose of the surgical procedure, be it resective or palliative, as this primes expectations of postsurgical outcome in the surgery team, patient, and family [6]. To maximize patient recovery, consensus about what constitutes a reasonable set of expectations is required [13] and should canvass the notion of surgical "cure" versus "control," with the former invoking the more stringent outcomes of complete seizure freedom and cessation of all AEDs after surgery [14]. These notions should be considered relative to what constitutes becoming "well" in the daily life of the patient and what changes that might invoke for the patient and family after surgery [15].

This latter point highlights a dominant focus in the research literature to identify predictors of seizure outcome, with less attention to factors that predict other outcomes, such as AED cessation, mortality, and cognitive, psychiatric, or psychosocial functioning [14]. Ideally, we should aim for more differentiated profiles of surgical candidacy that identify patients at varying levels of risk across a range of outcomes, including patients at "high risk" for poor outcomes across multiple measures. This view promotes a broader search for the range of preoperative neurobiological and psychosocial markers of postsurgical risk or resilience. It requires knowledge of the interplay of factors that create the greatest or least risk for a given patient, promising a more sophisticated clinical understanding of "surgical candidacy" and the differing trajectories of outcome that may follow.

3.2. Promising Areas of Research and Young Investigators

Riki Matsumoto

Refining our understanding of surgical candidacy: In vivo investigation of cortico-cortical networks

The recording of cortico-cortical evoked potentials (CCEPs) using an in vivo electrical tract tracing method is an exciting new presurgical technique developed by Dr. Riki Matsumoto and colleagues at Cleveland Clinic and Kyoto University. It promises to refine our understanding of surgical candidacy, first through a more precise and tailored evaluation of the seizure network in each individual patient, and second through greater understanding of the functional systems of the brain involved. Both are important for improving our ability to identify patients at high risk for poor surgical outcomes across multiple outcome measures.

3.2.1. Cortico-cortical evoked potentials

A better understanding of seizure networks as well as the mechanisms involved in human higher cortical functions requires a detailed knowledge of neuronal connectivity. Little progress, however, has been made in the understanding of the neuronal connectivity of the human brain until very recently. The majority of knowledge of cortico-cortical connectivity has come from extrapolation from invasive trace-tracking studies performed in nonhuman primates. As it relates to the higher cortical functions of humans such as language, studies performed in nonhuman primates are less relevant. In vivo connectivity studies in humans have only recently begun using noninvasive methods, such as diffusion tensor tractography (DTT). This technique enables visualization of the "in vivo dissections" of association and commissural fibers, and has confirmed the presence of major white matter fasciculi in the living human brain [16,17]. These pathways, however, are determined solely by mathematical calculations of anisotropy of water molecules. Thus, further work is needed to understand the anatomical organization of cortico-cortical networks using different modalities, including CCEPs [18,19].

By means of subdural electrodes implanted for presurgical evaluation, Matsumoto and colleagues [18,19] applied electrical pulses (0.3-ms duration, frequency of 1 Hz, alternating polarity, 1–12 mA) directly to the cortex, and obtained evoked cortical potentials from adjacent and remote cortical regions by averaging the electrocorticogram time-locked to the stimulus onset ($20–30 \times 2$ trials). In contrast to diffusion tractography, the CCEP technique has the advantage of tracking the inter-areal connectivity physiologically, providing directional as well as temporal information. Clinically, the CCEP method is highly practical because it can be done (1) easily with an online