

Interview

The importance of surgery for epilepsy



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■ How did your career become focused on neurobiology & specifically epilepsy?

In college I was interested in the brain and behavior; what it is about the human brain that is responsible for human behavior. When I went to medical school, I decided to do a MD and a PhD at Stanford in this area. At the time, my intention was to become a neurosurgeon because I thought that this would give me the best opportunity to work with the human brain. I did my thesis work with Frank Morrell in the department of neurology and, in the course of those studies, I became well versed in basic research on epilepsy, and ended up in neurology rather than neurosurgery.

When I got to my neurology residency at Einstein, everybody assumed that I knew about clinical epilepsy. Since there was no epileptologist at Einstein at the time, they looked at me as the epilepsy expert, so I had to become one quickly.

My career has involved basic research, clinical research and clinical practice; they inform each other. Initially, it is difficult to do research and practice, but as time goes on the clinical work helps you to identify the most relevant basic research areas and the basic research helps you to find ways to aid your clinical practice. Ultimately, it becomes much easier when you do both.

■ How significant is the burden of epilepsy? Have any measures been taken to increase awareness of this burden?

I think a lot has to be done to raise consciousness regarding epilepsy in general. The American Epilepsy Society has joined with the Epilepsy Foundation and a number of other organizations that are stakeholders in epilepsy, including the National Institute of Neurological Disorders and Stroke, and the Centers for Disease Control, to form a working group called Vision 20:20, which is trying to raise consciousness in the USA about epilepsy as a serious disorder.

The WHO has performed studies on the global burden of epilepsy, not just based on mortality, but on disability. Using disability-adjusted life years (the number of years lost as a result of disability or premature death), epilepsy accounts for 1% of the global burden of disease. This is equivalent to breast cancer in women and lung cancer in men. The reason for this is that many people have epilepsy for a lifetime, whereas breast and lung cancer are diseases that affect people at the end of life. Therefore, the life years that contribute to the burden are relatively short for cancer and very long for epilepsy.

Depression and other affective disorders, Alzheimer's disease and other dementias, substance abuse, and epilepsy are the



top four primary disorders of the brain. The other three disorders get far more attention in the press and are allocated more resources. For this reason, Vision 20:20 is trying to find ways that we can educate people about epilepsy and the need for additional resources.

■ **Much of your research has focused on the role of surgery for treatment of epilepsy. What place does surgery have within the range of treatments for the condition?**

Epilepsy surgery is probably the most under-utilized of all accepted therapeutic interventions in the field of medicine. I do not know of any intervention shown to be as effective as epilepsy surgery that is so infrequently used. If you consider that approximately 40% of people with epilepsy have seizures that are not controlled by medication and that a quarter of these are potential candidates for surgery, which is probably an underestimate, this means that 10% of people with epilepsy are potential surgical candidates. This is a huge number of people – 300,000 in the USA – but the evidence suggests that no more than 3000 surgeries are performed per year in the USA, and this has remained constant for two decades. I do not think the figure of 1% is much different in any other industrialized country in the world.

■ **Do you think surgery should be performed earlier?**

In addition to the fact that epilepsy surgery is rarely utilized, when it is, it is too often too late to make a difference in the patient's quality of life. The average time between onset of epilepsy and surgery is 22 years [1]. For surgically remediable conditions, seizures usually begin in childhood and adolescence. When disabling seizures occur during adolescence and early adulthood, people with epilepsy do not always acquire the interpersonal and vocational skills necessary to lead an independent life. When these people have surgery many years later, even though they do become seizure free, many remain dependent on their families and on society.

For this reason, there has been a big push for early surgical treatment. In 2001, there was a randomized trial of epilepsy surgery published by Sam Wiebe [2].

Based on that study and a meta-analysis that clearly demonstrated the superiority of surgical intervention over continued medical treatment for pharmacoresistant temporal-lobe epilepsy, the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons, published a practice parameter [3] that recommended temporal-lobe surgery as the treatment of choice for pharmacoresistant temporal-lobe epilepsy. They suggested that surgery be performed early in order to avoid irreversible psychological and social disability.

Our group has just completed a study that will be published in *Neurology* shortly [4], looking at the duration from diagnosis to the time of referral to our epilepsy center; that is, the time it takes the patient and physician to decide that they want a second opinion about surgery. We studied this for a 4-year period a few years before publication of the randomized controlled trial and the practice parameter and for a 4-year period a few years after publication of the parameter, and there was absolutely no change. On both occasions the duration from diagnosis to referral was 18 years, indicating that the publications have had no impact on community concepts of the important role of surgery.

■ **Why do you think surgery is not a popular treatment option?**

We have been struggling for decades to understand why there is such reluctance on the part of physicians and patients to consider surgical treatment. I think this is caused by various misconceptions. There is a general assumption that epilepsy is a benign disorder, which is untrue: people die from it. There is also a misconception about the risk of surgery. The mortality among patients with uncontrolled epilepsy is somewhere between five- and ten-times higher than it is in the general population, whereas the mortality rate from surgery is less than 1%.

One of the problems is that when a person is diagnosed with epilepsy, they may have four or five seizures every week, and when they are treated with drugs, the seizures may be reduced to once a month, or even two or three times a year. The family and physicians see this as such an



improvement that they do not consider other options; but even this frequency of seizures causes disability in that there are many things the patient cannot do, including driving a car. The seizures also put them at risk of sudden unexplained or accidental death. With surgery, they could become seizure free.

Despite the fact that there have been dozens of books and hundreds, if not thousands, of papers published in the last two decades, we just have not done a good job of educating primary-care physicians, general neurologists and patients about the role of surgery in epilepsy, and its safety and efficacy.

A major problem is that community neurologists feel that it is up to them to make a decision as to whether the patient is a surgical candidate or not. They often incorrectly decide that a patient is not a surgical candidate and never send them to an epilepsy center. I have talked to neurologists here in my own city, who still believe that if patients do not have a lesion on MRI or if they have interictal EEG spikes that are bilateral, they are not a surgical candidate, which is, frankly, wrong. The message should be that all patients who continue to have disabling seizures after two drugs have failed, owing to inefficacy and not intolerance, should be referred to an epilepsy center. Even if patients are not surgical candidates, the people at these centers are specifically trained to identify other possible treatments. As soon as seizures begin to interfere with work, school or interpersonal relationships, patients should be referred to a specialized epilepsy center.

■ What does the surgical procedure involve & what are the risks to patients?

There are a variety of surgical procedures carried out. A major development in the past few decades has been the recognition that there are many different types of surgeries appropriate for different types of epilepsy.

The most common procedures are various forms of anteromesial temporal resection for temporal-lobe epilepsy – the most common and most refractory form of epilepsy, and also the most amenable to surgical treatment. Most procedures are now carried out using microsurgical techniques,

so the safety and efficacy of surgery has been greatly improved during the last few decades. In patients undergoing this type of surgery, 70–90% can expect to have a seizure-free outcome.

The mortality rate from this surgery is much less than 1% and morbidity is between 3 and 8%, with half resolving within a year. A common consequence of this surgery is a minor visual-field defect, which, with microsurgical techniques, is now less common. The defect usually presents in the upper quadrant of the visual field and most patients will not even be aware of this defect, unless they are basketball players or jet pilots.

The most serious concern is when patients have normal verbal memory prior to surgery and their language function is on the side of the brain that will be operated on – usually the left hemisphere. Surgery can then result in a reduction in the patient's verbal memory capacity. However, most patients with epilepsy in the language-dominant temporal lobe already have a verbal memory deficit, so in these cases, there is no additional deficit.

If patients do not have verbal memory loss prior to surgery on the language-dominant temporal lobe, then the risk for this deficit needs to be taken into consideration, particularly if surgery is performed early. On the other hand, if surgery is not performed and seizures continue, then verbal memory capacity is likely to be reduced anyway.

Other less standardized, so-called 'tailored,' resections can be performed when the epileptogenic region is outside the mesial temporal lobe. This often involves resection of a lesion identified on MRI with variable amounts of neocortex, but it is always necessary to carry out electrophysiological testing to ensure that the lesion is, in fact, the cause of the seizures. Even when there are no identifiable lesions, electrophysiological studies – either intraoperative or chronic invasive recording – can identify the location and extent of the epileptogenic region, permitting successful surgical resection. When a specific epileptogenic lesion is identified, seizure freedom can be as high as 70–90%, while patients without such structural lesions may only have a 50% chance of becoming seizure free postoperatively.



There are procedures that are carried out in very young children who have severe epilepsy that is caused by lesions limited to one hemisphere. These children go on to have devastating outcomes; they can die from the condition or they usually end up in institutions with mental retardation and other neurological disorders. Removal of a hemisphere, or part of a hemisphere, can make approximately 80% seizure free and, in most patients, when seizures are eliminated, surgery reverses the developmental delay and all of the psychological and social problems that are caused by seizures. These people can then go on to live relatively normal lives. Most of these patients already have hemiparesis, so doing this type of surgery does not introduce an additional neurological deficit. In many cases, the deficit improves so that, for example, if the individual has severe weakness in their leg and post surgery they no longer suffer seizures, they will eventually be able to walk. These patients were largely written off in the past so this is a lifesaving technique that is increasingly being used to produce very gratifying results.

There are a variety of additional palliative surgical procedures that mostly involve disconnection, and reduce seizure frequency and severity but do not necessarily render patients seizure free. These include procedures such as corpus callosotomy, multiple subpial transection and deep-brain stimulation.

■ What techniques have been developed to better evaluate patients for surgery?

Evaluation involves an MRI scan, EEG and an in-patient video EEG in order to see where seizures are coming from. In addition, most centers will perform a PET scan, intracarotid amobarbital test and neurocognitive testing, which also help determine the safety of the planned resection.

There are many new tests available, including magnetoencephalography, functional MRI, diffusion tensor imaging and ictal SPECT. These techniques now allow more accurate noninvasive identification of surgical candidates. Even if we fail in these noninvasive tests, if we have hypotheses regarding two or three potential epileptogenic regions (the area that should be removed in order to render a patient seizure

free) then we perform invasive EEG testing. If we think seizures are deep in the brain (e.g., mesial temporal) these tests involve stereotactically implanting depth electrodes. If we think the problem is in the neocortex then we use subdural electrodes or strips. We have a very high chance of identifying patients who are surgical candidates using these more invasive tests.

■ What do you think will be the key developments in epilepsy surgery over the next 10 years?

I think that continued advances in neuroimaging will be crucial, but most important will be the development of biomarkers that can measure epileptogenicity. Assessment for surgery would be greatly improved if we had a noninvasive biomarker that could tell us which areas of the brain were epileptogenic. For instance, if there were neuroimaging markers for the epileptogenic region then we would not need to carry out other expensive testing or record seizures.

There is a potential imaging biomarker – α -methyl-tryptophan – that has been identified by PET. There has not yet been sufficient work performed on this marker, but there are some encouraging data, suggesting that it might soon be possible to identify the area of the brain affected by epilepsy with an α -methyl-tryptophan PET scan.

Another potential biomarker that has received a lot of interest is pathological high-frequency oscillations. These are very brief bursts of EEG activity in the range of 100–600 Hz. Studies suggest that they are very accurate in determining the epileptogenic region that needs to be removed. The problem is that, so far, these high-frequency oscillations can only be measured with electrodes placed directly in or on the brain. Ideally, we would like to be able to record these events noninvasively.

Even using invasive methods to record high-frequency oscillations could save a considerable amount of time and money as we would not need to implant electrodes and then wait for seizures to occur. We could simply put the electrodes in and determine where the epileptogenic regions are in just a few hours.

Currently, there is substantial interest in biomarkers for epilepsy and they may, in fact, provide a major breakthrough in the

next decade to greatly increase the efficacy and reduce the cost and risk of surgery, and also increase the number of people who become surgical candidates.

Financial & competing interests disclosure

Original research cited by the author was supported by P01 NS02808, R01 NS33310 and U01 NS42372 from the NIH. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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