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Relieving the burden of intractable epilepsy in India and other developing countries: the case for two tier epilepsy centers

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Abstract

India, with a population of over 1 billion, is likely to have more than a million patients with intractable epilepsy of whom 1/3 to 1/2 are likely to be benefited by Epilepsy Surgery. However, the total number of patients operated till date would not be very much more than 1,200. The Indian situation more or less mirrors the developing country scenario with approximately only 26 of 142 developing countries having at least one epilepsy surgery center. The major reason behind this dismal situation is the unavailability of epilepsy surgery in most parts of the country because epilepsy surgery is deemed to be possible only in massive institutions. One way to overcome this is to have a two-tiered epilepsy surgery program. The first tier would consist of multiple small epilepsy surgery centers equipped with only a high-quality MRI, inter-ictal scalp EEG, standard microneurosurgical facilities and staffed with well-trained epilepsy surgeons and epileptologists. These centers should be able to deal with unilateral temporal lobe epilepsy and single structural lesions in non-eloquent cortex which constitute around 70% of cases suitable for epilepsy surgery in developing countries. The rest of the 30% can be referred to the few advanced centers. This strategy would popularize epilepsy surgery and make it more available at a lower cost. The proposal is based on the belief that a high-quality MRI in itself is adequate pre-operative evaluation for clear-cut unilateral temporal lobe epilepsy and single structural lesions.

THE ENORMITY OF THE "SURGICAL GAP"

India, with a population of over 1 billion, is likely to have, on a conservative estimate, more than a million patients[1] with medically intractable epilepsy. One-third to one-half of these million patients is likely to be significantly benefited by epilepsy surgery. In contrast to this evident requirement for epilepsy surgery, the total number of patients operated in the country till date would not be very much more than 1,200. The "Surgical Gap" therefore is immense. The economic burden of epilepsy in India[2], direct and indirect, is 88.2% of GNP per capita, 0.5% of the GNP, and most of it would be due to intractable epilepsy.

The Indian epilepsy surgery situation more or less mirrors the developing country scenario. An article by Wieser and Silfvenius[3] revealed that in 1999, only 26 of 142 developing countries had at least one epilepsy surgery center despite the fact that developing countries are home to around 90%[4] of the people with epilepsy worldwide.

REASONS BEHIND THE SURGICAL GAP

In India, there are two most important centers providing active epilepsy surgery service, and have demonstrated very good results. The All India Institute of Medical Sciences (AIIMS)[5], India's premier medical institution in New Delhi, caters mostly to the Northern part of India. The other being the Sri Chitra Tirunal Institute[6] in Trivandrum, another prominent super-specialty institution, which is located at the extreme south of the country. Evidently, there is a large portion of the country in between, especially in the East and North-East without close access to facilities for epilepsy surgery.

This absence of epilepsy surgery facilities in vast portions of the country is one of the major reasons behind the lack of awareness among referring physicians and even neurologists about the benefits of epilepsy surgery. In situations that they remotely know about epilepsy surgery, because of no exposure to the same, their fears about surgery are exaggerated. This lack of

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awareness thereby leads to non-referrals or delayed referrals. The mean duration of suffering from intractable epilepsy before being operated in India has been quoted to be as long as 15 years.[7] But, these patients who were operated even after 15 years were the more fortunate ones, compared to the tens of thousands who never came to know about epilepsy surgery. This is not unexpected given the fact that in a report from Tampa in USA[8], the duration of seizures before being seen at the epilepsy surgery center averaged 18 years (range 2-58 years). Thirty-nine percent of their patients were self-referred without having been offered surgery by their neurologists and 14% had been specifically advised by their neurologists not to consider surgery.

In contrast to the "non-marketing" of epilepsy surgery, all the new and costly antiepileptic drugs (AEDs) are extensively marketed even in the interiors of the country. This leads to referring physicians persisting with medical treatment in various permutations and combinations for inordinately long periods. This is in spite of the fact that the chance that new AEDs, including levetiracetam, will control these intractable patients is at best around 16%[9], as compared to 70-90%[3,6,14] with epilepsy surgery. In fact, some studies quote a lower success rate for levetiracetam of around 3.7% to 6.2%.[10,11] Moreover, with delayed surgery and a fixed lifestyle, successfully termination of seizures by surgery may have little impact on the quality of life of the patients.[12] Because of these reasons, there should be early identification of medically refractory epilepsy and prompt referral for surgical treatment.[13] Based on economic cost, it has been shown that in a developing country like India, one-time successful surgery is almost 5 times[6] less expensive than a lifetime of unsuccessful medical treatment.

INCREASED AVAILABILITY AND DECREASED COST OF SURGERY BY DEVELOPMENT OF A TWO-TIERED EPILEPSY SURGERY PROGRAM

The "big center" strategy may have inadvertently become the hindrance to popularizing epilepsy surgery. Epilepsy surgery has till date been performed only in big centers in India, such as the two mentioned above. Both these centers[5,6] have protocols designed on the format of leading epilepsy surgery centers of the world. However, in developing countries such as India, such big centers can only be few and far between.

Therefore, to popularize epilepsy surgery, the protocols have to be simplified so that they can be implemented in centers with fewer resources. Bigger centers would still be required to manage the more complicated cases. Essentially, what we are recommending is development of a two-tiered epilepsy surgery program.

WHAT SURGICAL PROCEDURES ARE POSSIBLE AT THE FIRST TIER?

The biggest portion of the epilepsy surgery burden in developing countries such as India is temporal lobe epilepsy (TLE), predominantly mesial temporal sclerosis (MTS). Of the 394 epilepsy surgery undertaken at Sri Chitra[7], 370 were antero-medial temporal lobectomy (AMTL) for refractory TLE. This is also true worldwide, where MTS constitutes more than half of all patients with refractory epilepsy.[14] It is also well accepted that lesional TLE in adults, including MTS, is often refractory to AEDs.[15]

The surgical procedure for TLE is fairly well standardized, though the technique (whether AMTL or selective amygdalohippocampectomy, and the approach for the latter) varies between surgeons and between centers. The surgical procedure itself for TLE does not require too much more than standard microneurosurgical facilities. Thus, surgery for TLE can be performed at smaller centers with good results provided the neurosurgeons are well trained at epilepsy surgery.

Similarly, the surgical procedure for lesional epilepsy, whether temporal or extratemporal (commonly tumors including gangliogliomas and DNET's and occult vascular malformations) in non-eloquent cortex can be done, with excellent results, at such smaller centers equipped with standard microneurosurgical facilities and staffed with epilepsy surgery trained microneurosurgeons.

Therefore, as regards surgery for TLE and lesional epilepsy, it is imperative that centers active in epilepsy surgery ensure that their residents and fellows are adequately trained at epilepsy surgery during the course of their training. The 2 centers actively involved in epilepsy surgery in India train a minimum of 10 neurosurgeons every year to serve in various other parts of the country. Even if 5 of them going to 5 areas of the country initiate epilepsy surgery, it would result in significant growth of epilepsy surgery services in the country.

The first tier of multiple smaller epilepsy surgery centers all over the country which we propose should be staffed with well-trained neurologists and neurosurgeons who have had a very good exposure to epilepsy surgery at the previously mentioned two premier institutions of the country. Foreign training would be helpful in broadening their perspective but only foreign training without proper exposure to the Indian scenario might just serve as a mental impediment in "creatively cutting corners". This term is loaned from Nayel[16] but is extremely apt to describe what we propose.

Neurologists and epilepsy surgeons located at the first tier should be able to determine that their patients have true seizures and not pseudo-seizures and should also be able to determine that they have had a fair trial with the right conventional drugs at the maximum tolerated doses with good compliance.

IS PRE-OPERATIVE EVALUATION THE STUMBLING BLOCK FOR DEVELOPMENT OF EPILEPSY SURGERY AT THE FIRST TIER CENTERS?

The problem of developing epilepsy surgery at smaller centers lies not so much in the surgical procedure but in the pre-operative evaluation. Even the so-to-say shortened protocols which AIIMS and Sri Chitra[5,6] use are far too much to be replicated in other areas of the country. AIIMS uses MRI, SPECT, video-EEG, inter-ictal EEG and neuropsychological evaluation for all cases. Sri Chitra uses MRI, video-EEG, inter-ictal EEG and neuropsychological evaluation for all cases and WADA for left-sided cases.

Among all the above listed pre-operative evaluation tools, only high-quality 1.5T MRI and inter-ictal scalp EEG are easily available in other major cities of the country. All the other tools are in a way epilepsy surgery specific and are therefore unlikely to find favor with funding agencies, be it government, non-governmental organizations or private. From the perspective of the government and non-governmental organizations, precious resources in a developing country like India should be used behind more pressing primary health problems such as malnutrition, sanitation, tuberculosis, and diarrhea. From the perspective of the private sector, investment in epilepsy surgery is non-profitable compared to investment in, for example, cardiac surgery.

So, how far we can go with only high-quality 1.5T MRI and inter-ictal scalp EEG is an important question.

A HIGH-QUALITY MRI IS THE CORNERSTONE OF PRE-OPERATIVE EVALUATION AT THE FIRST TIER CENTERS

The patients in the first tier centers should undergo an inter-ictal scalp EEG and a high-quality 1.5T MRI. Needless to say, epilepsy surgeons should play a very important role in setting the MRI protocol for Intractable Epilepsy and in also interpreting the scans because neuroradiologists would be harder to find. But, this is not a problem at all because good neurosurgeons tend to be good neuroradiologists as well!

The MRI protocol[17] should at least include inversion recovery sequences (especially fluid attenuated inversion recovery sequences, FLAIR) in addition to standard T1 and T2 sequences. It should also necessarily include thin coronal slices perpendicular to the axis of the hippocampal formation. Gadolinium should be used if there is any suspicion of a structural lesion other than MTS. Sometimes, more sensitive MRI protocols may be available including 3D volumetric image acquisition using radio-frequency spoiled gradient-recalled echo (SPGR) sequences which suppress the signal of CSF, has good gray-white differentiation and allows reformatting in various planes due to its 3D nature.[19]

Analysis of the MRI at the first tier centers can be done solely with visual inspection and does not require complex volumetry or relaxometry because the objective at this tier is only to pick up obvious cases. MTS[17] can be identified by atrophy of the mesial temporal structures accompanied by a higher signal on FLAIR or T2 sequences.

Caution must be exercised not to identify MTS only on the basis of a bigger temporal horn on one side because side to side temporal horn asymmetry is well described. Head rotation can lead to false interpretation, either positive or negative because the coronal images will intersect the two hippocampi at different sites on the anteroposterior length of the hippocampi. Anatomical landmarks useful in determining side-to-side symmetry with respect to the anatomical coronal plane are the internal auditory canals or the crura of the hippocampal fornices.[18] Sometimes, subependymal heterotopia on one side may be mistaken as normal and the other side as having MTS. Focal dilatation of the hippocampal fissure may occur in normal individuals. This normal variant may produce increased T2 signal in the hippocampal formation and may present an appearance identical to that of MTS. Moreover

side to side asymmetry of the high signal of the choroid plexus on FLAIR may be interpreted wrongly. Shading artifact in which an entire hemisphere is brighter than the other will result in one hippocampus having a brighter T2 signal, on a purely artifactual basis which can however be recognized if the brighter T2 signal is noticed on the whole of that hemisphere including the hippocampus.

Movement artifacts and CSF pulsation artifacts can degrade T2 images. However, this is more of a problem with old generation scanners. One also needs to keep his/her mind open to the possibility of bilateral MTS because visual analysis tends to compare one hippocampus with the other.

DISTINGUISHING WHAT CANNOT BE PURSUED AT THE FIRST TIER CENTERS

Henceforth, we will discuss the issue from the point of view of the MRI findings. Patients with a normal looking MRI, with dual lesions, with any suspicion of bilateral MTS, with cortical dysplasias (malformations of cortical development), gliotic patches, diffuse or bihemispheric pathology, hypothalamic hamartomas, multiple tubers, structural lesions in eloquent cortex are not be treated at the first tier and must be referred to the more well-equipped centers.[20]

Sometimes, it might seem reasonable to think that a patient with a single focus of cortical dysplasia or gliosis with seizure semiology explainable by the location can be safely operated. But, it is probably not recommended in view of the fact that both cortical dysplasia and encephalomalacia /gliosis can be multiple and a single foci detected on a MRI scan might just be the tip of the iceberg and multiple foci might become evident on a higher resolution MRI. Therefore, in cases of cortical dysplasia[20] or gliosis[20,21], confirmation of electrical and functional abnormality of the structural lesion is imperative and needs to be taken care of at more well equipped epilepsy surgery centers.

Basically, what can be possibly be pursued at the first tier of epilepsy surgery centers is unilateral TLE and single structural lesions (commonly tumors including gangliogliomas and DNET's and occult vascular malformations) in non-eloquent cortex. It is well established that single epileptogenic structural lesions in non-eloquent cortex, clearly identified on a MRI, can be safely removed with a margin as surgical treatment of epilepsy without any more investigations.[20,22,23]

IS MRI ADEQUATE PRE-OPERATIVE EVALUATION FOR UNILATERAL MTS?

Cukiert *et al*[24] reported 100 patients with intractable epilepsy who had undergone corticoamygdalohippocampectomy for unilateral MTS diagnosed solely by visual inspection of a high-quality MRI. None of them had undergone any other investigations, including Video-EEG, for localization. Eighty nine patients had a Class I outcome while the other 11 had a Class II outcome. Of the 155 cases operated until December 2003 at AIIMS[25], 99 patients had undergone AMTL for TLE. Of the 99, 90 had clear-cut unilateral MRI localization. Of these 90, 13 had discordant video-EEG localization and 4 had discordant SPECT localization. However, all 90 patients ultimately underwent surgery on the MRI-identified side irrespective of SPECT or video-EEG discordance. Interestingly, all the patients with SPECT or video-EEG discordance had a Class I outcome. The overall Class I outcome was 84.7% among all the 90 patients.

We strongly believe that for patients with intractable epilepsy, unilateral temporal lobe pathology easily identified on MRI does not necessarily require re-confirmation, for the purpose of surgical localization, by other tests such as video-EEG, SPECT and PET. There is no harm in re-confirmation but for non-controversial MRI, re-confirmation is probably not a must. Cukiert *et al*[24] opined that ruling out pseudoseizures remains the only indication for a video-EEG in this category of patients.

WADA IS NOT A NECESSITY IN MEMORY LOCALIZATION FOR UNILATERAL MTS

The other objection to operating for TLE only on the basis of a MRI is memory, especially for left-sided cases. Language localization for TLE does not really alter surgical approach for an AMTL or selective amygdalohippocampectomy.

The only test with a reasonable degree of accuracy for memory localization is the WADA, though the validity of the WADA in predicting memory post-operatively by mimicking the effects of surgery has been doubted in many quarters. An internal carotid artery injection leads to extensive fronto-temporal inactivation while only a portion of the head of the hippocampus gets perfused from the anterior circulation. The rest of the hippocampus is supplied by the posterior cerebral artery which is normally not injected.

There are quite a few centers today in the world that operate for TLE without a WADA.[5] In a review of multiple papers published on the subject of memory and intelligence following temporal lobe epilepsy surgery[5], Sanyal Sujoy concluded that patients with imaging evidence of pathology in the unoperated temporal lobe as well as patients with lesser evidence of pathology in the operated temporal lobe are the ones at risk of memory deterioration, thereby also pointing to the fact that imaging evidence of pathology is a good indirect indicator of the functional status of the temporal lobes (which is what the WADA aims to measure). The absence of obvious imaging pathology in the contralateral temporal lobe as well as non-controversial imaging evidence of pathology in the temporal lobe of surgical interest implies a functional contralateral temporal lobe without requiring a WADA.

Sanyal Sujoy *et al*[5] also reported a prospective neuropsychological study of 25 right handed adults operated for TLE (13 right, 12 left) without a WADA with imaging evidence of only unilateral pathology and no imaging evidence of pathology in the opposite temporal lobe. Patients undergoing surgery on the non-dominant temporal lobe demonstrated significant cognitive improvement associated with good seizure outcome. In view of the possibility of reversible cognitive dysfunction involving the contralateral functional temporal lobe due to the influence of an epileptogenic ipsilateral lobe, we feel that freeing this contralateral functional lobe from the deleterious influence of intractable epilepsy by successful surgery may have been the key behind their cognitive improvement. A good seizure outcome did not however translate into cognitive improvement for patients undergoing surgery on the dominant temporal lobe (though they demonstrated no deterioration). This is probably because the functional right temporal lobe of these patients has a lesser reserve than the left, in terms of memory processing.

In summary, among patients with intractable epilepsy, if unilateral MTS is clearly identified on a high-quality MRI with no suspicion of any contralateral pathology, a standard AMTL or selective amygdalohippocampectomy can be performed safely with good results without any other investigations for seizure localization or memory localization.

SURGICAL PROCEDURES THAT ARE NOT POSSIBLE AT THE FIRST TIER CENTERS

Surgical procedures not to be tried at this first tier of epilepsy surgery centers are vagal nerve stimulation, multiple sub-pial transection, surgery for infantile spasms and multi-lobar resection. Patients with no identifiable resective pathology are suitable for vagal nerve stimulation and the first tier is not well equipped enough to conclude the same. For obvious reasons, patients requiring multiple sub-pial transection need to be evaluated by functional mapping, functional MRI and therefore are not suitable for the first tier centers. Similarly, patients requiring multi-lobar resection require much more extensive pre-operative evaluation.

Corpus callostomy and hemispherotomy are two procedures to be used with caution at the first tier centers and depend entirely on the experience of the epilepsy surgeons and epileptologists running the program. Corpus callosotomy can be used for catastrophic epilepsy, drop attacks, sudden generalized seizures without localization but has to be balanced against the fact that what is not localizable with only a MRI and inter-ictal scalp EEG may become localized with more advanced evaluation protocols. Hemispherotomies[20,26] can be performed with great benefit, for children with large epileptogenic lesions on MRI involving primarily one hemisphere with significant neurological impairment on the contralateral side, without any other investigations. However, surgeons attempting a hemispherotomy should have the necessary confidence in successfully executing the procedure.

CONCLUSIONS

The author is of the opinion that unilateral TLE and single structural lesions in non-eloquent cortex can be easily taken care of at the proposed first tier of multiple small epilepsy surgery centers. The centers should be equipped with high-quality MRI, inter-ictal scalp EEG and standard microneurosurgical facilities. They should be staffed with well-trained epilepsy surgeons and epileptologists who have a deep understanding of the issue of intractable epilepsy in a developing country scenario.

Unilateral TLE easily identified on MRI constituted around 58%[25] of patients operated at AIIMS, in North India. At Sri Chitra in South India[7], it was much higher. It is a reasonable estimate that unilateral TLE, along with single

structural lesions in non-eloquent cortex, account for around 70% of cases suitable for epilepsy surgery in developing countries. It is this population which needs to be targeted and taken care of by the proposed first tier of multiple ES centers all over the country. The rest of the 30% can be referred to the advanced centers.

This strategy should make epilepsy surgery more widely available at a lower cost. Decentralization of epilepsy surgery should help to make more physicians and general public aware of the benefits of epilepsy surgery. It is also possible that when the benefits of epilepsy surgery become more widely known, funding for further development of the program will also increase. The strategy involves starting the program with the bare minimum and slowly forging ahead, instead of not establishing the program because the facility for managing the more complicated cases is not available or affordable.

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