Role of Surgery in Pediatric Epilepsy

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Twenty five percent of patients with intractable epilepsy have surgically remediable epilepsy syndromes. This article reviews the treatment paradigm for pediatric epilepsy and also the indications, methods, and surgical options for the subgroup of patients with surgically remediable epileptic disorders based on our experience in the management of these children. The article also discusses the rationale for offering surgery and the timing of surgery in these patients. The study of surgically remediable epilepsy can best be divided into focal, sub hemispheric, hemispheric and multifocal epileptic syndromes. These syndromes have both acquired and congenital etiologies and can be treated by resective or disconnective surgery. The surgical management of these conditions (with the exception of multifocal epilepsy) provides Engel's Class 1 outcome (complete seizure freedom) in approximately 80% of children. The consequences of seizure freedom leads to a marked improvement in the quality of life of these children. The benefits to society, of allowing a child to grow to adulthood with normal cognition to earn a livelihood and contribute actively to society, cannot be understated.

Key words: *Epilepsy surgery, Focal epilepsy, Hemispheric epilepsy, Intractable epilepsy*

The current treatment strategies available to treat pediatric epilepsy include use of conventional antiepileptic drugs (AED), new AEDs, ketogenic diet, vagus nerve stimulation and epilepsy surgery. Monotherapy (treatment with a single AED) is recommended wherever possible. 'Add-on' therapy should be considered when attempts at monotherapy with AEDs have failed. After adequate

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Correspondence to: Prof. Roy Thomas Daniel, Department of Neurological Sciences, Christian Medical College, Vellore, Tamil Nadu, India. E-mail: roy@cmcvellore.ac.in pharmacotherapy, 20-25% have persistent seizures refractory to medication(1). There cannot be a single definition for "intractable" epilepsy that will suit all situations. Definitions of intractability must be individualised to the patient. However, the commonest definition for intractable epilepsy is when seizures continue despite maximally tolerated doses of more than two AEDs, occurrence of an average of one seizure per month for ≥ 18 months with no more than a 3 month seizure free period during these 18 months(2). Of patients deemed to be intractable, approximately 50% are estimated to have surgically remediable epilepsy(1).

Who is a Candidate for Surgery? (Fig.1)

Children who present with epilepsy are evaluated in the epilepsy clinic and are then started on appropriate medical therapy. When deemed intractable, they are evaluated by the presurgical laboratory. The evaluation includes a study of the seizure semiology, neurological examination, multiple electroencephalogram (EEG) examinations (video telemetry), magnetic resonance imaging (MRI) and neuropsychological evaluation. The focus of the examination is to identify a surgically remediable epilepsy syndrome with good electro-clinico-radiological concordance. If the lesion that is producing epilepsy can be safely removed without incurring deterioration in the functional status, the patient is considered for epilepsy surgery. However, if there is no concordance in investigations in the presurgical laboratory evaluation, the patient enters a Phase II evaluation which may include prolonged invasive EEG monitoring, nuclear medicine studies [positron emission tomography (PET) and single photon emission computerized tomography (SPECT)] and a WADA (Sodium amylobarbital) test. Surgery is offered if concordance is obtained and the risk of incurring functional deterioration is considered minimal or acceptable.

Surgically Remediable Pediatric Epilepsy Syndromes

The surgical treatment of pediatric epilepsy is



Fig. 1. Flow chart for management of epilepsy

better understood by subdividing this group based on their location and extent into four subgroups: hemispheric, sub-hemispheric, focal and multifocal. In each subgroup, the etiologies may be of congenital or acquired origin.

1. Hemispheric Epilepsy

Infantile hemiplegia seizure syndrome (IHSS)

It refers to unilateral paralysis noticed in early childhood as a result of various pathologies affecting one hemisphere in utero or perinatally. Two-thirds of the patients will develop seizures at some time during childhood, which may be refractory to antiepileptic medication and leads to progressive developmental retardation. Imaging reveals hemispheric atrophy with a dilated ventricular system. There may be evidence of middle cerebral or internal cerebral artery infarction and/or associated porencephalic and subarachnoid cysts (*Fig. 2*)

Rasmussen's encephalitis

This is a chronic childhood encephalitis manifesting with intractable epilepsy and progresses almost always to hemiplegia and cognitive dysfunction. 50% of patients have a preceding viral illness, though a clear viral etiology has not been documented. An autoimmune basis has also been suggested. These patients typically present with focal motor seizures though other forms are also known and half of these patients eventually progress to epilepsia partialis continua. Though this illness is typically unilateral, there have been sporadic reports of bilateral disease. Radiological and functional imaging reveal the slowly progressive unilateral destructive nature of the disease (*Fig. 3*).

Sturge Weber Syndrome (SWS)

Patients with SWS (encephalotrigeminal angiomatosis) usually present with progressive hemiparesis, seizures and mental retardation. Radiological studies show the pial angiomatosis and intracranial calcifications (*Fig. 4*). Both localised and diffuse forms of the disease are known but they are almost always unilateral. Patients with focal disease may have normal intelligence and may be candidates for localised resections. On the other hand, diffuse hemispheric SWS often progresses rapidly to marked developmental retardation, which is related to damage to the hemisphere of venous origin.

Disorders of neuronal migration

Hemimegalencephaly is a hypertrophic neuronal migrational disorder that present with an early onset of seizures, mental retardation, hemiparesis



Fig. 2. T2W Axial flair MRI images of a 4 year-old-girl with Infantile Hemiplegic syndrome. Figure 2a showed atrophy of the left temporo- occipital lobes with a small and maldeveloped crus cerebri which indicated a remote insult. Figure 2b showed atrophy of left frontal and parietal lobes with marked atrophic changes in the perisylvian region (in the arterial supply of the left middle cerebral artery).



(*a*)

(b)

Fig. 3. T2W Axial MRI images of a 6-year-old boy with Rasmussen's Encephlitis. Six months after the onset of the illness (Fig. 3a), MRI scan showed T2 weighted hyperintensities of all lobes in the left hemisphere with early atrophic changes. MRI scan done a year later (Fig. 3b) showed that the left hemisphere had T2 weighted hyperintensities that had increased markedly compared to the earlier scan with more cortical atrophy and ventricular dilatation.



Fig. 4. T2W Axial MRI image of a 7-year-old boy with Sturge Weber syndrome. The MR image showed right hemispheric atrophy, gyriform calcification and leptomeningeal angiomatosis predominantly in the right parieto-occipital lobe.

and frequently hemianopia. They can present with a large head and may be associated with linear nevus sebaceus or chronic linear nevi. Radiological imaging shows a markedly enlarged hemisphere with a thickened cortical mantle (Fig.5). On pathological examination, pachygyria is seen and typical microscopic features include loss of cortical architecture, giant neurons, neuronal heterotopia and gliosis. On the other hand, diffuse hemispheric non-hypertrophic cortical dysplasia occurs less frequently and manifests with a smaller hemisphere with a variety of migrational abnormalities.

Other hemispheric syndromes

A variety of acquired pathologies can affect predominantly one hemisphere. These include cerebrovascular accidents due to thrombo-embolic phenomena due to heart disease or children undergoing heart surgery or extracorporeal membranous oxygenation. In developing countries, post meningoencephalitic sequelae form not an uncommon cause for hemispheric epilepsy. Cerebral infarction secondary to severe dehydration and severe hypotension can also present likewise. Cranial traumas, brain damage secondary to massive intracranial AVM bleeds are more infrequent causes. Selection criteria for hemispheric epilepsy surgery(3)

- (*a*) Medical intractability is an absolute requirement but long trials of anticonvulsants may not be necessary as most often the seizure frequency is very high.
- (*b*) Contralateral hemiparesis should be present. Patients with hemispheric epilepsy usually present with weakness of distal musculature of the upper and lower limbs. An examination shows marked weakness of "finger opposition" and inability to do "foot tapping". The power in the proximal musculature is quite good. If hemispherectomy is done prior to maximal hemiplegia (Grade 0/5), digital dexterity and foot tapping may be lost but the patient will be able to walk and use proximal muscles of the upper limb. In rare cases, this loss of function may have to be accepted as the cost of control of debilitating seizures and cognitive decline.
- (c) Neuro-developmental retardation is usually present due to the interference of frequent seizures on the developing normal hemisphere. However patients with severe neurodevelopmental retardation are not good candidates for surgery.



Fig. 5. MRI images of a 4-year-old boy who presented with Hemimegalencephaly. T1W Axial (Fig. 5a) and T1W Inversion Recovery Coronal (Fig. 5b) MRI scan showed an enlarged right hemisphere with thickened cortical mantle, distorted ventricular anatomy and widened gyri.

(*d*) The hemisphere contralateral to the hemiplegia should be demonstrated by radiological [MRI/ computerised tomography (CT)] and functional (scalp EEG / EEG video telemetry) imaging to have a unilateral diffuse abnormality. More importantly the remaining hemisphere should be normal to have a good result following surgery.

Surgical Intervention and results for hemispheric epilepsy

The hemispheric epilepsy syndromes are currently treated in most centres with disconnective techniques. We prefer to treat these patients with peri insular hemispherotomy which(4-6) is a lateral hemispherotomy approach. Variants of this approach include hemispheric deafferentation, transopercular hemispherotomy and transsylvian keyhole functional hemispherotomy(7-9). The other approach described is the vertical hemispherotomy approach of Delalande(10). The seizure outcome after surgery is classified according to Engel's classification.

(*i*) Class I includes the ones who are completely seizure free in the year after surgery.

- (*ii*) Class II includes ones with rare seizures only (> 90% reduction in seizures).
- (*iii*) Class III with the ones who would continue to have seizures but have shown worthwhile improvement (75-90% reduction in seizures)
- (*iv*) Class IV included those who had no improvement or became worse after surgery

Analysis of data of the published series of hemispherotomy and our present series (2006) are stated in *Table I*. An analysis of our series of pediatric disconnective hemispheric epilepsy surgery also showed an 89% Engels Class I outcome with very minimal complication rate(12). Studies by our group to analyse the subgroups of hemispheric epilepsy with reference to seizure outcome following surgery showed that the best candidates were children with infantile hemiplegia seizure syndrome and Rasmussen's encephalitis(13,14).

2. Subhemispheric Epilepsy

Multilobar surgeries (resective or disconnective surgery) have been increasingly used in the last 10

	Series	Ν	Seizure outcome	Engel's Class 1	Follow up	Complications
1	Villemure(4) (1995)	11	Class I: 9/11 Class II: 2/11	82%	0.3-3 years	Hydrocephalus 1 (9%)
2	Schramm(7) (1995)	13	Class I: 11/12 Class II: 1/12	92%	Mean 1 year	Hydrocephalus 1 (8%)
3	Delalande(10) (2000)	53	Class I: 41/52 Class II: 10/52 Class IV:1/52	80%	1-8 years	Death 1 (2%) Hydrocephalus 10 (20%)
4	Shimizu(9) (2000)	34	Class I: 18/27 Class II: 2/27 Class III: 6/27 Class IV:1/27	67%	>1 year	Grave Morbidity 1(3%) Hydrocephalus 5 (15%)
5	Kestle (11) (2000)	16	Class I: 14/16 Class II: 2/16	88%	Mean 3 years	Nil
6	Schramm(8) (2001)	20	Class I: 14/16 Class III:1/16 Class IV:1/16	88%	Mean 3.8 years	Death 1(5%) Infection 1 (5%) Temporal Cyst 1 (5%)
7	†Villemure et al (12) (2006)	43	Class I: 34/38 Class II: 4/38	89%	1-12 years	Death 1 (2.3%) Distant haemorrhage 2 (4.6%) Hydrocephalus 1 (2.3%)

TABLE I- Case Series of Hemispherotomy with Seizure Outcome and Complications. The Seizure Outcome is Based on Engel's Seizure Outcome

† Senior author's series

years though these surgeries amount to less than 5% of all epilepsy surgeries(15,16). When the epileptogenic zone encompasses large areas of the temporal, parietal and occipital lobes and spares the central and frontal areas (Fig. 6a,b), multilobar surgery is indicated. The decision for this surgery is dependant on good concordance between the imaging (MRI, CT, nuclear studies), EEG, clinical and neuropsychological evaluations and a clear localization of the lesion to the unilateral affected region. The indications for multilobar resections are the same as for hemispheric epilepsy, the pathology being more localized to involve a part of the hemisphere. The presence of residual voluntary motor function of the contralateral distal musculature, *i.e.*, finger opposition and foot tapping is the indication for multilobar surgery preserving eloquent uninvolved cortex. We prefer to perform this multilobar surgery using a disconnective approach(17). Speech should be a concern in dominant posterior multilobar surgery. In our experience with treatment of left sided lesions, all patients had congenital lesions and consequently had language functions residing in the right hemisphere. This was suspected on the basis of the seizure semiology, neuropsychological examination, and more on the basis of the nature and location of the radiological abnormalities. Analysis of available data of multilobar surgery for subhemispheric epilepsy is stated in *Table II*. In our case series of 11 patients who underwent multilobar surgery, Engel's Class I outcome was obtained in 82% of cases with no mortality or significant morbidity(18).

3. Focal Epileptic Disorders

The evaluation of epilepsy in this group should focus on the identification of surgically remediable focal epileptic lesions. In the last decade, these lesions are being increasingly identified with advent of improved neuro-imaging. The frequently recognized focal lesions are

(a) Neoplasms (indolent): Ganglioglioma (Fig.7a)



(a)

(*b*)

Fig. 6. MR images of a 11-year-old boy who presented with complex partial seizures of 8 years duration with no motor deficits. T2WAxial Flair (Fig. 6a) and T1W Sagittal Flair (Fig. 6b) images showed a temporo-parieto-occipital atrophic lesion resulting in a porencephalic cyst.

Series	Ν	Follow-up	Outcome
Wyllie ⁽¹⁹⁾ (1998)	38 (Adults and children)	1-7.4 years	Engels I 62.5%
Koszewski ⁽²⁰⁾ (1998)	93 (Adults and children)	_	Engels I 53%
† Daniel et al (unpublished)	11 (Children)	7.6 years	Engels I 82%

TABLE II-Case Series of Multilobar Cortical Resections with Seizure Outcome

† Senior author's series

and dysembryoplastic neuroepithelial tumor (Fig.7b); (b) pre, para and postnatal traumatic, vascular (Fig.7c) and inflammatory lesions; (c) gliosis (traumatic or surgical); (d) neuronal migrational disorders: (Fig.7d) focal cortical dysplasia, microdysgenesis, grey matter heterotopia and schizencephaly; (e) tuberous sclerosis; (f) Sturge-Weber syndrome (focal); (g) mesial temporal sclerosis (Fig.7e); (h) hypothalamic hamartoma (Fig.7f).

The decision to operate again rests on concordance of evidence between clinical, radiological and electroencephalic data that emerges from the pre-surgical evaluation and that the patients will not have a neurological deficit after surgery. The results of surgery are in general excellent for the vast majority of patients with hardly any morbidity. Analysis of data of the published series of focal cortical resections is stated in *Table III*. In a study conducted by us previously on 15 children with cortical dysplasias (12 patients focal and the others sub hemispheric), analysis of seizure outcome showed that (mean follow-up period 1.4 years), 14 children were seizure free (93%), and therefore classified as Engel's class I, while 1 child developed a few seizures 7 months after surgery and therefore classified as Engel's class II(23). According to the parents, all children with behavioural problems before surgery showed

Fig. 7. MRI scan images of focal epilepsia



Fig. 7a. T2W Axial flair MR scan showing a hyperintense lesion in the right medial part of the temporal lobe (Ganglioglioma)
Fig. 7b. T1W Axial Gadolinium MR image showing a left frontal hypointense lesion with a posteriorly placed enhancing component (Dysembryoplastic neuroepithelial tumour).



Fig. 7c. T2W Coronal MR image showing a right medial temporal lesion with variegated hyperintensities (Cavernoma).
Fig. 7d. T2W Axial MR image showing a left frontal lesion with poor gray white differentiation and T2 weighted hyperintensity (Cortical dysplasia).



Fig. 7e. T2W Coronal flair MR image showing evidence of volume loss in the right medial temporal region. There is enlargement of the temporal horn and altered signal intensities in the region (Mesial temporal sclerosis)
Fig. 7f. T1W sagittal MR image showing a hypointense non enhancing lesion arising from the hypothalamus (Hypothalamic hamartoma).

IABLE III –Case Series of	Focal Cortical	Resections with	Seizure Outcome

Series	Ν	Follow-up	Outcome
Kloss ⁽²¹⁾ (2002)	68	6m - 9 years	Engel I + II = 60%
Kral ⁽²²⁾ (2003)	14	Mean of 50 months (adult + children)	Engel I + II = 94%
†de Ribaupierre, <i>et al.</i> ⁽²³⁾ (2003)	15	2m - 3 years	Engel I 93%

† Senior author's series

an improvement with better concentration and abilities at school activities. There were no procedure related morbidities or neurological complications in this series.

4. Multifocal Epileptic Disorders

Both medical and surgical treatments of this group pose a formidable challenge. The common syndromes that present with multifocal epilepsy are Lennox Gastaut syndrome, West syndrome and bihemispheric sequelae of trauma/vascular insults and progressive neurological diseases. Presurgical evaluation in this group will exclude the possibility of a resective or disconnective surgery as described earlier. The majority of these patients are also significantly developmentally challenged. This group is generally treated with polypharmacy and/ or diet alterations. The place for a surgical intervention in this group is limited to palliative treatment. In an earlier study of 11 children in our institute with multifocal epilepsy after anterior/total

What this Study Adds

• For patients with "surgically remedial epilepsy", surgery should be offered as a procedure of choice rather than as a treatment of last resort.

callosotomy, 60% had good improvement and 30% had a worthwhile improvement following surgery. 50% of patients in this group had transient mutism as part of the disconnective syndrome(24). No patient had cessation of seizures though the disabling generalized seizures reduced greatly. The seizure type most responsive to callosotomy was "drop attacks" (atonic or tonic seizures). The results of callosotomy in other series in literature are also similar in its efficacy as a palliative measure towards some generalized seizure type(25). Vagal nerve stimulation has in the last decade largely replaced callosotomy in many centers due to similar seizure outcomes without the added cognitive deterioration possible with callosotomy. However in India, this is still an expensive option in comparison to callosotomy.

Timing of Surgery

The effects of seizures, anticonvulsants, post ictal state and interictal discharges on cellular events during cerebral maturation in a child with intractable epilepsy is deleterious to the normal maturation of the brain. In addition, the development of regions of the brain that are uninvolved by disease, does not reach its true potential due to disturbed social integration and loss of schooling. At the same time, neurological worsening after epilepsy surgery is a possibility. The chances of neurological worsening after surgery in children is lowered because insults sustained inutero or in childhood stimulate the development of brain functions in the normal hemisphere. There has also been evidence to support that in cases where the seizures started later in childhood, early surgical intervention helps the shift of functions especially language to the contralateral side. However, the exact age at which the normal plasticity of the brain ceases to transfer brain functions has not yet been defined. In view of all these factors, early surgery is advisable in cases

of catastrophic childhood epilepsy especially in certain syndromes that are known to progress to intractable epilepsy and developmental retardation (Rasmussen's syndrome and Sturge-Weber syndrome). In some cases, if the deficits are not maximal, it may be better to wait till they do become maximal.

Conclusion

Over 80% of children with focal, sub hemispheric and hemispheric epilepsy syndromes achieve an excellent seizure outcome following surgery. Development of functions in the residual brain, leads to a "catch up" of cognitive functions and psychosocial skills. Early diagnosis of intractability and investigations directed towards the identification of surgically remediable epilepsy syndromes prior to the cessation of neural plasticity, should be the cornerstone of management of patients with intractable epilepsy.

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