

Disconnective Surgery for Refractory Multilobar and Hemispheric Epilepsy, A Study of 38 Children

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Introduction

Intractable epilepsy secondary to multilobar and hemispheric pathologies is more prevalent in young children [1]. The negative impact of such seizures on neurological, intellectual and psychosocial development, as well as the risk of irreversible consequences in later life, has been well documented [2-4]. There is also a higher risk of mortality in these patients, often from status epilepticus and sudden unexpected death [5]. As a significant proportion of multilobar and hemispheric epilepsies are due to developmental malformations and in-utero insults, seizures often manifest very early in life. The vulnerability of the developing brain can lead to an increased frequency and severity of seizures, especially epileptic spasms and status epilepticus. The immaturity of the brain also increases risk of seizures being resistant to anticonvulsant medications [6].

Whilst the need to pre-empt the above mentioned deleterious effects justifies early surgical control of intractable seizures, extensive resective surgery in young children with multilobar and hemispheric pathologies poses unique challenges [7-9]. Especially with extensive developmental malformations, where aberrant brain anatomy can lead to difficulty with intraoperative anatomic orientation. The friable nature and abnormal vascularity of brain parenchyma can pose technical difficulties with surgery, cause extensive blood loss and result in suboptimal surgery. The small blood volume, delicate physiological reserves and relatively high body surface area in young children increases vulnerability to hypovolaemia, coagulopathy, hypothermia and electrolyte disturbances, with prolonged surgery [10,11]. There is also a higher risk of postoperative hydrocephalus, delayed haemorrhage, and haemosiderosis with extensive hemisphere resections [12,13].

The rationale for disconnective techniques in multilobar and hemispheric pathologies is based on the principle that complete isolation of the epileptogenic pathology from the healthy brain, achieves the same result in terms of seizure control as extensive resection. At the same time, a less invasive approach with a reduced exposure, less brain tissue disruption, and minimal brain tissue resection will lead to a concomitant reduction of operating time and mitigate the aforementioned risks in young children [14-17].

The primary aim of this study was to determine the safety and efficacy of disconnective procedures for refractory multilobar

and hemispheric epilepsy, as defined by the risk of complications and by long term seizure outcome, in children with drug resistant epilepsy. We also sought to determine if surgical control of epileptic seizures, would translate to improvements in the quality of life of both patients and families - a secondary outcome goal of prime importance.

Materials and Methods

Patient Population – This is a retrospective cohort study of a consecutive series of 38 children with refractory multilobar and hemispheric epilepsy, 26 of whom underwent functional hemispherotomy and 12 of whom who posterior quadrant disconnection at our institution, by a single surgeon, from January 2006 to January 2020. These procedures comprised 24% and 11% respectively of all epilepsy surgery procedures conducted at our institution during the same period.

Presurgical Evaluation and Candidate Selection

- **Clinical Evaluation** - was performed by a Consultant Paediatric Neurologist with experience in selection of patients for epilepsy surgery, with evaluations of seizure semiology, development, and behaviour.
- **EEG Evaluation** - involved Interictal and Video EEG monitoring, interpreted by the same Consultant Paediatric Neurologist.
- **Radiological Evaluation** - involved 3-Tesla MRI using a dedicated epilepsy imaging protocol in most patients, in the rest with 1.5 T MRI. Positron-emission tomography (PET) was performed in some patients, when considered helpful to define the epileptogenic zone.
- **Establishment of Refractory Nature of Seizures** - Patients were refractory to at least 2 recommended anticonvulsant medications at appropriate dosage.
- **Joint Presurgical Evaluation and Patient Selection** - Concordance of presurgical data to localize epileptogenic zone, the safety and efficacy and goals of a specific epilepsy surgery procedure for a given patient was established, prior to disconnective surgery by multidisciplinary evaluation. Clinicoradiological concordance of seizure origin was of prime importance in candidate selection.

Those with EEG evidence of independent seizure origin from the contralateral hemisphere and major imaging abnormalities

in the contralateral hemisphere were excluded. The presence of subtle abnormalities, such as reduction in the volume of the unaffected hemisphere or mild T2 white matter hyperintensities were not excluded from selection. In patients in whom presurgical evaluation was difficult, an opinion was sought from an eminent Paediatric Neurologist from Royal Children's Hospital Melbourne, Australia.

Surgical procedure

Presurgical planning of the disconnective procedure was performed using the I Plan (Brainlab) system. A single surgeon conducted all epilepsy surgery procedures. A Brain lab Image Guidance System (IGS), a Leica operating microscope, and ultrasonic aspiration were used in all patients. Posterior quadrant disconnection was performed as described by Daniel et al 2007 and Dorfer et al 2013 [18,19]. Functional hemispherotomy was performed using the periinsular technique as described by Villemure et al 2006 [20].

Outcome Measures

Postoperative complications

Adverse post-surgical complications recorded included death, prolonged impairment of consciousness post-surgery, major unexpected neurological deficit, symptomatic postoperative haematoma, infection and hydrocephalus. Less adverse events included prolongation of hospital stay, acute postoperative seizures and prolonged pyrexia without sepsis. Expected neurological deficits were hemianopia and worsening of hemiparesis after functional hemispherotomy, deterioration of speech in some patients after dominant hemisphere disconnection and hemianopia after posterior quadrant disconnection.

Seizure freedom

The primary outcome measure of freedom from seizures was assessed using the Engel's classification of seizure outcome [21].

Quality of Life (QOL) Outcome

QOL of Patients - Changes in Quality of Life outcome after epilepsy surgery for patients was estimated based on following measures - Physical Functioning, Language, Social development, Emotional functioning, Social Interaction, Independence with activities of daily living, School performance, Hospital Visits, Anticonvulsant Drug (AED) Burden.

Grading of above measures was as follows, on a 5 point Likert Scale.

- Major improvement - a significant improvement of QOL
- Moderate improvement - a noticeable improvement of QOL
- Mild improvement – a mild, hardly noticeable improvement of QOL
- No Change
- Moderate deterioration a worsening from preoperative functioning but with some interference with QOL, but with ability to cope
- Major deterioration - a significant worsening from preoperative functioning, with significant interference with QOL.
- When a patient was not capable of determining the QOL, the caregiver assessed the outcome.

QOL of Caregivers - The caregiver was defined as the family member or guardian, responsible for provision of day to day care, antiepileptic drug provision, outpatient and emergency visits and provision of rehabilitation.

QOL of caregivers included overall impact on family functioning, time spent managing the patient, effect on occupation of parents, financial burden due to illness of patient, effect on social life of

family and overall satisfaction with epilepsy surgery. Grading of QOL measures of Caregivers was performed as for QOL of patients. Overall satisfaction after epilepsy surgery was graded as yes, no or not certain.

Statistical Analysis

The Chi-square test or the Fisher Exact test univariate analysis were used association analysis of seizure outcome/Engel Classification with Age of seizure onset, Age at surgery, Seizure -surgery interval and MRI defined pathology. The Chi-square test or the Fisher Exact test were used to determine the correlation between of QOL of patients and caregiver with seizure outcome/ Engel Classification, Age of seizure onset, Age at surgery, Seizure -surgery interval and MRI Epilepsy pathology. A p-value of 0.05 was used as the cutoff for statistical significance.

Results

Clinical Presentation (Table 1)

Table 1: Demographic, Clinical and EEG Characteristics (N = 38), no. (%)

Mean age at seizure onset (yrs)	1.8, SD ±2.5, 0.0–12.0	
Age at surgery (yrs)	Mean 7.9, SD 4.7	
	Distribution	
	<5 yrs	14(37%)
	10-15 yrs	12(32%)
Gender M/F	17/21	(55% Female)
Age at seizure onset(yrs)	Mean 1.1 (SD 2.3; Min,Max 0.1,12)	
	Distribution	
	<1 yr	30(79%)
	1-4 yrs	5 (13 %)
	5-9 yrs	2(5%)
	10-15 yrs	1(3%)
Seizure Characteristics		
	Focal onset	30 (79%)
	Generalized	4 (10%)
	Lateralization by seizure semiology	30 (79%)
Lateralization by EEG		
Interictal EEG	34(89%)	
Videotelemetry	31(81%)	

Demographic Characteristics

This study involved 38 patients younger than 18 years, who had undergone either functional hemispherotomy or posterior quadrant disconnection. Mean age at surgery was 7.9 years (Median 3.5), 14 patients being 5 years or younger and only 2 patients aged 15 years or older (Table 1).

Seizure Characteristics

The mean age of seizure onset was 1.1 years(Median IQR 0.3), with 35 (92%) being 5 years or younger at seizure onset. The most common AEDs were Clobazam (47%), Levetiracetam (45%), Vigabatrin and Carbamazepine (39%), Phenobarbitone (31%), Topiramate (31%), and Valproate (29%).

Seizure semiology demonstrated focal onset in 30 patients (79%). A generalized onset was evident in 4 and a mixed onset 1, in the rest seizure onset was inconclusive. Seizure semiology helped to

lateralize seizure origin in 30 patients (79%).

Neurological Manifestations

Cerebral dominance (as determined by hand preference) was evident in 25 patients (66%), with left dominance in 16. Developmental delay was evident in 37 (97%), learning disability in 37 (97%) and behavior problems in 13(34%) . Hemiparesis or hemiplegia evident in 27 (71%), speech was impaired in 31 (82%) of whom 9 were non-verbal. Impaired visual function was evident in 11 patients.

Interictal EEG

Interictal EEG showed lateralization (as determined by background abnormalities or epileptic discharges) in 34 patients (89%), and bilateral interictal discharges were evident in 4(10%) of the patients.

Videotelemetry (Ictal EEG)

Ictal EEG demonstrated a lateralized seizure onset in 31 patients (81%), and bilateral onset in 6(16%).

MRI and PET CT features

MRI Features

A 3T MRI was performed using an Epilepsy Specific Protocol in 26 patients (68%) and in the rest a 1.5T MRI was performed, using same protocol. The MRI was abnormal in all the patients. Dual pathology was evident in 3%.

PET CT

PET CT was helpful in 11 patients and was a critical factor in localization of epileptogenic zone in those with poor localization of seizures on EEG, with poor concordance between EEG abnormalities and the MRI and with poorly defined lesion margins with posterior quadrant pathology.

The Features of Epileptogenic Pathology Based on Presurgical Evaluation (Table 2)

Hemispheric pathology was evident in 26 patients (68%) and multilobar lesions in 12 (32%). The nature of the epileptogenic lesion based on MRI, is shown in Table 2. Developmental pathology was evident in 27 patients (71%).

Table 2: The nature of the epileptogenic lesion based on presurgical evaluation (N = 38) no. (%)

Developmental pathology	
Malformations of cortical development (Hemimegalencephaly, Multilobar dysplasia, Heterotopias	25 (65)
Neurocutaneous syndromes - Tuberosus sclerosis complex	2 (5.2)
Progressive pathology	
Rasmussen syndrome	1 (2.5)
Acquired pathology	
Perinatal insults	4 (10)
Stroke	2(5.2)
Infection	1(2.5)
Others	3 (8)

Table 3. Surgical Treatment and Long term outcomes . (N = 38) number (%)

Interval from Epilepsy Onset to Surgery	< 1 year	7(18)
	1 - 2 years	12(32)
	3-5 years	11(29)
	>5 years	8(21)
Type of disconnective procedure	Functional Hemispherotomy	26(68)
	Posterior Quadrant Disconnection	12(32)
Long Term Seizure control		
Duration of follow up		
For whole cohort	Mean 3.4 years ,SD 3.3	
>= 2 years	23 (61)	
>= 5 years	8 (21)	
Long term Seizure freedom (Engel's Classification)		
Class I, seizure free	28(74)	
Class Ia only auras	2(5)	
Class II >90% reduction	3(8)	
Class III 50-90% reduction	5(13)	
Class IV <50 reduction	0(0)	
Determinants of long term seizure outcome(Univariate analysis by Fisher's Exact Test)		
Age of seizure onset	p 0.048	
Age of at surgery	p 0.044	
Correlation between long term seizure control and improvements in Quality of Life (QOL)outcome of patients(Univariate analysis by Fisher's Exact Test)		
Changes in cognition	p 0.029	
Changes in language development	p 0.045	
Burden of antiepileptic drugs		

Correlation between long term seizure control and improvements in Quality of Life (QOL)outcome of caregivers(Univariate analysis by Fisher's Exact Test)

Overall impact on family functioning p 0.021

Delays to Epilepsy Surgery

Time from seizure onset to epilepsy surgery was 2 years or less in 19 patients (50%), 5 or more years in 11 (29%). In 24%, caregivers had misconceptions with respect to the safety and efficacy of epilepsy surgery, leading to delay with surgery.

Immediate outcome

There was no operative mortality. Unexpected complications were evident in 4 patients(transient hemiparesis in 2 patients after Posterior Quadrant Disconnection ,both of whom had delayed recovery). Two patients had prolonged pyrexia without evidence of infection after hemispherotomy. Anticipated neurological deficits were present in 22 patients (58%) and included worsening speech (when involving dominant hemisphere),hemiparesis and hemipanopia after hemispherotomy and hemipanopia after posterior quadrant disconnection.

Mean duration of hospitalization was 9.1 days. One patient developed postoperative hydrocephalus requiring placement of a ventriculoperitoneal shunt.

Long Term Outcome (Table 3)

The mean follow up was 3.4 years (2 or more years in 61%, and 5 or more years in 21%). The longest follow up was 13.2 years.

Two patients underwent reoperation. One patient for persistent seizures due to an incomplete frontobasal disconnection after hemispherotomy for hemimegalencephaly. This patient was seizure free after completion of the disconnection by reoperation. The other patient initially underwent posterior quadrant disconnection for what was considered posterior quadrant multilobar dysplasia. She developed late seizure recurrence and a repeat MRI showed dysplastic changes in the posterior frontal region. She then underwent a functional hemispherotomy and has been seizure free since.

Seizure Outcome (Table 3)

Engel's Class I outcome was achieved in 79%, at a mean follow up of 3.4 years. A 90% seizure reduction was achieved in 8%. Moderate to major improvements in the burden of antiepileptic drugs were noted in 75% post-surgery.

A Univariate analysis by Fisher's exact test demonstrated a significant correlation between seizure control and younger age of seizure onset (p 0.048) and earlier age at surgery (p 0.044) (Table 3). There was no correlation between seizure-surgery interval (p 0.485) and type of epileptogenic lesion ie. congenital vs progressive/acquired pathology (p 0.479).

QOL Outcome of Patients.

Moderate to major improvements in Quality of life of patients were noted as follows - Cognition 64%, Language development 35%, Physical function 50%, Social interaction 53% , Independence with activities of daily living 32% ,School performance 11%, the need for hospital visits/hospital admissions 82% and the Burden of antiepileptic drugs in 75%.

Deteriorations were noted only in a small minority and included language development (4%), physical function (14%), independence with activities of daily living (4%), school performance (4%) and an increase of the burden of antiepileptic medications (4%).

Univariate analysis showed a significant correlation between seizure control and improvements in 3 measures of QOL of Patients - improvements in cognition (p 0.029), improvements in language development (p 0.045) and improvements in burden of antiepileptic drugs(p 0.007). (Table 3)

Quality of life Outcome of Caregivers

Major to moderate improvements were noted in QOL of caregivers with respect to the measures of overall impact on family functioning (75%), time currently spent with patient (75%), effect of occupation of parents (61%), financial burden due to illness of patient (54%) and effect on social life and leisure of family (71%).

Univariate analysis showed a strong correlation between long term seizure control and improvements overall impact on family functioning(p 0.021) . (Table 3)

Overall Satisfaction with Epilepsy Surgery

Overall 35 caregivers (92%) were satisfied with outcomes in terms of seizure control and quality of life .

Discussion

This study involves a population of predominantly young children, who underwent major disconnective epilepsy surgery, by a single surgeon, with patient selection determined by a standardized presurgical selection protocol. These procedures comprised 24% and 11% respectively of all epilepsy surgery procedures conducted at our institution during the same period, a distribution similar to that reported in the ILAE study by Harvey et al [1]. However, our cohort had a much higher proportion of developmental pathology (71%). The mean age of seizure onset in our cohort was 1.1 years, with 92% being 5 years or younger at seizure onset, concurring with reported experience in children with hemispheric and multilobar pathologies [22,23].

Presurgical Evaluation

Our presurgical evaluation philosophy was based on non-invasive identification of the epileptogenic zone by clinical, EEG and High resolution MRI and supplemented by PET-CT. It is possible that more patients could have been selected for surgery if invasive preoperative mapping was added to the presurgical evaluation. However, such invasive monitoring is resource and manpower intensive and carries a small risk of complications. It was considered not to be cost effective in the situation that prevailed in our practice. Moreover, use of high resolution MRI and PET CT had led to a less frequent use of invasive monitoring.

Delays to Surgery

The epilepsy - surgery interval was less than 2 years in 50% of our cohort with 21% undergoing surgery 5 years after epilepsy onset. Delay to epilepsy surgery is also reported in more advanced countries, with a mean seizure duration of 5.7 years before surgery, in a worldwide study by ILAE [1]. In a very highly developed paediatric epilepsy surgery programme, the median delay from seizure onset to surgery was found to be 30 months [24].

This study found a delay in referral for multidisciplinary presurgical evaluation. Evaluation by a physician not trained in epileptology, suboptimal MRI leading to a delayed diagnosis, multiple and irrational trials of AED and seizure burden being considered "tolerable", contributed to such delays. Some children required repeated presurgical evaluations, due to discordant findings, which also led to delay. Some caregivers showed initial reluctance to proceed with surgery , due to misconceptions of deleterious effects of uncontrolled seizures and of benefits and risks of epilepsy surgery. These findings, mirror those in a more developed epilepsy surgery programme [24]. Longer waiting times for epilepsy surgery have been reported with state funded health care systems [25]. In our epilepsy programme, though surgery was performed in a private hospital, all patients who came from financially handicapped situations were funded by charity programmes, with little delay to surgery.

Epilepsy Surgery Procedures

Safety of epilepsy surgery in our cohort as demonstrated by zero mortality and paucity of unexpected postoperative neurological deficits, compares well with the largest reported series on safety of epilepsy surgery, in the literature [26]. In our cohort, only 2 patients required reoperation for seizure control and only one patient required a CSF shunt for hydrocephalus.

Seizure control

Engel's Class I seizure control was achieved in 79% of the cohort (Class I - 74%, and Class I a 5%), at a mean follow up period of 3.4 years. A measurable improvement in the AED burden was evident in 75%. These results compare favorably with reported results of

disconnective surgery. Rizzi et al [27], reported a 2 year and 5 year seizure freedom of 74.5% and 73.5 % respectively after posterior quadrant disconnection. Hu et al [28], in a meta-analysis of 1528 patients, showed a pooled rate of seizure freedom of 73% after hemispheric disconnection, with non-developmental aetiology, absence of generalized seizures, lateralized findings on interictal or ictal EEG and the absence of contralateral MRI abnormalities being predictors of seizure freedom. In our study however, a majority (71%) of patients had developmental pathology, but there was a low incidence of generalized seizures. Patients who had non-lateralized EEG findings and significant contralateral MRI abnormalities were not considered for hemispherotomy.

Quality of life (QOL) Outcome

Improvements in QOL of patients become important secondary goals of epilepsy surgery and a predominant concern of families, once seizure control is achieved.

QOL outcome of Patients

A main concern of caregivers is the risk of deteriorations in cognition and social interaction postsurgery. In our cohort, successful epilepsy surgery resulted in moderate to major improvements in improvements in most QOL-patient parameters. Patients who had intact function before surgery (especially those who had posterior quadrant pathology), an unchanged outcome is very satisfactory as the main goal is to preserve function. Deteriorations in QOL were noted only in a small minority. A strong correlation was evident between seizure control and improvements in measures of QOL of Patients, paralleling findings of an exhaustive meta-analysis [29]. Deteriorations of parameters of QOL were only noted in a minority. A significant correlation was evident between seizure control and improvements in cognition, language development and burden of antiepileptic drugs.

Quality of Life Outcome of Caregivers

Caregiver QOL is a relatively neglected field of epilepsy research. In this study, improvements in caregiver QOL were significantly correlated with control of seizures, paralleling findings of previous studies [30,31]. With some patients, there was no change in some caregiver QOL parameters, despite seizure control and significant improvements in overall impact on family functioning, effect on social life of family and overall satisfaction with epilepsy surgery. Such patients often required attention of caregivers and continued rehabilitation for persistent preexisting impairments.

Limitations of this Study

This is a retrospective study with limitations imposed by accuracy of record keeping. However, most relevant data was easily accessed. The seizure outcome and QOL outcomes were assessed prospectively. Assessments of QOL were subjective with limitations such as recall bias. However, most studies of QOL outcomes, involve subjective evaluations.

The low number of patients in different subgroups can influence statistical analysis for determinants of seizure freedom and QOL. The mean follow up period in this study was 3.4 years. There is a possibility of late seizure recurrence, which can affect outcomes.

Conclusions

Hemispheric and posterior quadrant disconnection was achieved with a degree of safety and efficacy comparable to those achieved in more advanced health care settings. A non-invasive presurgical evaluation protocol helped to limit costs of care, whilst still providing good outcomes. Seizure control translated into meaningful improvements in quality of life outcomes of patients as well as caregivers.

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