“LONG-TERM SURGICAL OUTCOME AND ITS PREDICTORS AFTER HEMISPHEROTOMY FOR DRUG RESISTANT EPILEPSY”

Dr. Nandana J

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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

"LONG-TERM SURGICAL OUTCOME AND ITS PREDICTORS AFTER HEMISPHEROTOMY FOR DRUG RESISTANT EPILEPSY"

Dissertation submitted in partial fulfillment of the rules and regulations for Post-Doctoral Fellowship in Electroencephalography

By

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(01/01/2024 to 31/12/2024)

Month and Year of Submission: December 2024

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DECLARATION BY THE STUDENT

CERTIFICATE

I Dr. Nandana J, hereby certify that I had personally carried out the work depicted in the thesis titled, "**LONG-TERM SURGICAL OUTCOME AND ITS PREDICTORS AFTER HEMISPHEROTOMY FOR DRUG RESISTANT EPILEPSY**". No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



Date: 26/12/2024 Dr. Nandana J

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: **Dr. Ashalatha R**

Division/ Department: Department of Neurology

This is to certify that **Dr. Nandana J**, Department of Neurology of this institute has fulfilled the requirements prescribed for the Postdoctoral fellow in Electroencephalography of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum. The thesis entitled, "**LONG-TERM SURGICAL OUTCOME AND ITS PREDICTORS AFTER HEMISPHEROTOMY FOR DRUG RESISTANT EPILEPSY** " was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date. Clearance was obtained from the Institutional Ethics Committee for carrying out the study.



Date: 30-12-2024 Dr. Ashalatha R

Forwarded:

This is to certify that the dissertation entitled '**LONG-TERM SURGICAL OUTCOME AND ITS PREDICTORS AFTER HEMISPHEROTOMY FOR DRUG RESISTANT EPILEPSY'** is a bonafide research work done by **Dr Nandana J**, Post doctoral fellow in Department of Neurology, in partial fulfillment of the requirement of Postdoctoral fellowship in Electroencephalography.

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Date: 30-12-2024

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Dr. Nandana J

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LIST OF ABBREVIATIONS

Sl No	Abbreviation	Full Form
1	DRE	Drug-resistant epilepsy
2	EEG	Electroencephalography
3	VEEG	Video electroencephalography
4	IEDs	Interictal discharges
5	MRI	Magnetic Resonance Imaging
6	ASM	Antiseizure medication
7	APOS	Acute post-operative seizure

SYNOPSIS

Purpose: Hemispherotomy is an effective surgical approach for drug-resistant epilepsy with hemispheric epileptogenic lesions. The study aimed to determine the surgical outcome and its predictors in patients undergoing hemispherotomy for drug-resistant epilepsy and compare the outcome between the pediatric age group and above.

Methods: This is a single-center retrospective study. The relationship between the post-surgical outcome and clinical, demographic, EEG, and MRI brain characteristics were assessed using logistic regression. Also, classified patients according to their age, duration of epilepsy and assessed each patient's postoperative seizure outcome.

Results: 150 patients, mean age at surgery 11.21 $\pm$ 6.39 years, mean duration of seizures at time of referral 5.88 $\pm$ 5.34 years and at surgery 7.86 $\pm$ 6.15. 89 patients (59.3%) were of age less than 12 years (pediatric group). Most common pathology was Porencephalic cyst (33 patients, 30%), and MRI showed contralateral pathology in 15 patients (10%). EEG showed lateralized IEDs in 59 patients (39.3%) and ipsilateral ictal onset in 66 patients(44%). 71.3% were seizure-free and 78% had Engel class I outcome at last follow-up with mean follow-up of 8.42 years. Acute postoperative seizures (APOS), (OR 3.08; CI 1.23-7.69; p-value:0.016), and contralateral slowing in post-operative EEG at 1 year (OR 7.64; CI 3.25- 17.97; p-value:0.000) were independently predictive of poor seizure outcome. In survival analysis, the probability of seizure freedom was comparable between pediatric age and above, however, it was significantly higher in patients with epilepsy duration < 5 years (70% vs 50%; p value 0.047).

Conclusion: The presence of APOS and contralateral slowing in post-operative EEG are key determinants of poor seizure outcomes. There is no difference in seizure outcome with regard to age at surgery,however, those with shorter epilepsy duration had a better outcome. This emphasizes the need to bridge the surgical treatment gap by ensuring prompt referrals and addressing obstacles preventing epilepsy surgery.

INTRODUCTION

1. INTRODUCTION

Hemispherectomy is an effective surgical approach for medically intractable epilepsy in children with multilobar or hemispheric epileptogenic lesions, such as encephalomalacia, Rasmussen encephalitis, and malformation of cortical development (1,2). This procedure provides 70-90% Class I Engel seizure control when performed in properly indicated patients (1,3). This has replaced the more invasive hemispherectomy, the latter is associated with significantly higher rates of bleeding, hydrocephalus, cerebral hemosiderosis, and subdural collections.

Given the rarity of hemispherotomy surgery, few studies have exclusively assessed their surgical outcomes. This procedure provides 70-90% Class I Engel seizure control when performed in properly indicated patients (1,3). This has replaced the more invasive hemispherectomy, the latter is associated with significantly higher rates of bleeding, hydrocephalus, cerebral hemosiderosis, and subdural collections. Although the timing of therapeutic intervention differs depending on the underlying disease, early surgical intervention is desirable. The various predictors for poor outcome identified in earlier studies include pathologic etiology, notably with hemimegalencephaly patients achieving the lowest rates of seizure freedom, associated developmental abnormalities, bilateral MRI abnormality, generalized tonic clonic seizures and acute postsurgical seizures (4). In a meta-analysis of 56 studies, it was found that the pooled seizure free rate was 73% (11). And patients with an epilepsy etiology of developmental disorders, generalized seizures, nonlateralization on electroencephalography, and contralateral MRI abnormalities had reduced odds of being seizure-free after surgery(11).

The present study aims to analyze the predictive factors of long-term seizure outcome following hemispherotomy in our patient population and thus to improve the selection of appropriate candidates, choice of the optimal surgical strategy and the overall clinical management. And, to investigate on how early to consider hemispherortomy in these patients by comparing of outcomes between those who underwent surgery in the age group of upto 12 years and more than 12 years.

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

Hemispherotomy is an important surgical procedure for hemispheric disconnection, performed to treat intractable epilepsy associated with unilateral large epileptogenic lesion with contralateral neurological impairments, and if the preoperative evaluation confirms seizure onset in the lesioned hemisphere(Perucca et al) (5). Hemispheric epileptogenic lesions are usually characterized by a high frequency of seizures and propagation of epileptic discharges to the healthy hemisphere. The aim of a hemispherotomy is postoperative seizure freedom as well as complete disconnection of the affected hemisphere. It consists of corpus callosotomy and dissection of projection fibers into the internal capsule.

The different techniques of disconnection include the peri-insular hemispherotomy (PIH) (6), the vertical parasagittal hemispherotomy (7), and the trans-sylvian keyhole hemispherotomy (8). The selection process for hemispherotomy in patients with hemispheric epilepsy needs to be focused on identifying a uni-hemispheric epileptic syndrome. The evaluation consists of a detailed history and clinical examination, high-resolution magnetic resonance imaging (MRI) of the brain and multiple scalp electroencephalograms (EEG), and video-EEG monitoring (9).

A large proportion of the candidates for hemispherotomy have multiple developmental and cognitive impairments that at least partly stem from a common pathophysiology with the epilepsy. The common etiologies include developmental diseases (e.g., cortical dysplasia and hemimegalencephaly), acquired diseases (e.g., trauma, stroke, and infections), and progressive diseases (e.g., Rasmussen encephalitis and Sturge-Weber syndrome) (10).

Given the rarity of hemispherotomy surgery, few studies have exclusively assessed their surgical outcomes. This procedure provides 70-90% Class I Engel seizure control when performed in properly indicated patients (1,3). This has replaced the more invasive hemispherectomy, the latter is associated with significantly higher rates of bleeding, hydrocephalus, cerebral hemosiderosis, and subdural collections. Although the timing of therapeutic intervention differs depending on the underlying disease, early surgical intervention is desirable. The various predictors for poor outcome identified in earlier studies include pathologic etiology, notably with hemimegalencephaly patients achieving the lowest rates of seizure freedom, associated developmental abnormalities, bilateral MRI abnormality, generalized tonic clonic seizures and acute postsurgical seizures (4). In a meta-analysis of 56 studies, it was found that the pooled seizure free rate was 73% (11). And patients with an epilepsy etiology of developmental disorders, generalized seizures, nonlateralization on electroencephalography, and contralateral MRI abnormalities had reduced odds of being seizure-free after surgery(11).

In the study by Chandra et al in 2008 (12), they compared the two techniques for hemispherotomy performed either through a trans-cortical trans-ventricular route (Delalande) or through a perisylvian access (Villemure) among nineteen cases of intractable epilepsy. The seizure free outcome was 94% in the study group and both the techniques were found to be equally effective. In another study from India by Panigrahi et al (3) which studied twenty one children who underwent either Delalande's vertical para-sagittal hemispherotomy (VPH), or lateral peri-insular functional hemispherotomy, and they found that at last follow up 90.5% patients were seizure free; there was no difference between the groups for seizure freedom. And improved quality of life in epilepsy (QOLIE) scores was observed in 80.0% of the lateral peri-insular functional hemispherotomy group and 87.5% children of vertical para-sagittal hemispherotomy .

Non-lateralizing epileptiform (NLE) activity on preoperative scalp electroencephalograph (EEG) (9), i.e., bilateral independent spiking, generalized discharges, and contralateral slowing, was believed

to predict poor seizure control (13) in such patients leading to the utilization of interical/ictal single-photon emission computed tomography (SPECT) or positron emission tomography (PET) for further evaluation before proceeding with surgery. However, data from a few studies indicate that EEG findings are not always predictive of seizure outcomes (9,14). Even though EEG plays a central part in the evaluation of candidates for hemispheric epilepsy surgery. However, the exact prognostic value of the interictal and ictal findings, in particular, their location in relation to the operated hemisphere and their evolution from preoperatively to postoperatively, is not well understood, with variable and, sometimes, contradictory conclusions between different studies(9,14) .

Given the rarity of hemispherotomy surgery, there is only scanty data regarding their surgical outcomes and predictive factors. The three studies published from India had small size (19 cases (12), 23 cases (3) and 45 cases (9) respectively). While most the studies done from various centres across the world mostly looked at surgical outcome less than 18 years of age, there are few studies on patients exclusively at children upto 12 years of age (childhood age group, (15)), but the sample size was small. Hemispherotomy being an epilepsy surgery with 70-90% Engel class I outcome, the earlier the surgery the better should be the norm. However, data regarding comparison between patients upto 12 years and above are not available.

Our study would provide a comprehensive representation of hemispherotomy patients- their surgical and functional outcomes and its predictors; from a larger sample size especially of Indian scenario. Thus, to improve the selection of appropriate candidates, the choice of the optimal surgical strategy and the overall clinical management. This will also aid in diagnostic counseling, prognostication, and treatment in this subgroup of patients with refractory focal epilepsy.

AIMS AND OBJECTIVES

3. AIMS AND OBJECTIVES OF THE STUDY

The aim of this study was to determine the long-term seizure outcome and its predictive factors in patients who have undergone hemispherotomy in our centre with the following objectives:

1.To identify the factors determining the seizure outcome.

2.To improve the selection of appropriate candidates in future based on the above observations.

3.To investigate the difference in outcomes between those who underwent surgery in the age group less than 12 years and above (pediatric versus adults).

METHODOLOGY

4. METHODOLOGY

STUDY DESIGN: Observational retrospective study

STUDY SETTING: R Madhavan Nayar centre for comprehensive epilepsy care, Sree Chitra Tirunal Institute for medical sciences and technology

RECRUITMENT PERIOD: 2000-2023

SUBJECT/PARTICIPANT SELECTION

Patients with drug resistant epilepsy who underwent hemispherotomy with a follow up of at least 1 year post-surgery was taken up for study by retrospective chart review from a prospectively maintained cohort of patients who underwent epilepsy surgery at the R Madhavan Nayar centre for comprehensive epilepsy care at SCTIMST. The consecutive patients who fulfill inclusion and exclusion criteria were recruited.

NUMBER:

i)Total number: 160

ii) Sample size determination: Being a retrospective study carried out on a prospectively maintained cohort, the proposed sample size is 160. The rationale for the quoted sample size was that, being a retrospective review, the total number of patients who underwent hemispherotomy surgery for drug resistant epilepsy during the proposed study period was around 160 as verified. Hence this number was considered

iii) Sampling method : Retrospective chart review

iv)What proportion of them will be women: No such sex wise selection is intended or planned

(v) From where they recruited: retrospective chart review from a prospectively maintained cohort of patients who underwent epilepsy surgery at the R Madhavan Nayar centre for comprehensive epilepsy care at SCTIMST

ELIGIBILITY:

Inclusion Criteria:

1. Patients with drug resistant epilepsy who underwent hemispherotomy
2. Patients with a follow up of at least 1-year post-surgery

Exclusion Criteria:

1. Patients with follow up of less than 1 year
2. Patients without adequate clinical details, presurgical evaluation data

RECRUITMENT:

Retrospective chart review from a prospectively maintained cohort of patients who underwent hemispherotomy at the R Madhavan Nayar centre for comprehensive epilepsy care was done. Presurgical as well as post-surgical data of all the eligible patients was collected including the information from the latest follow up. Hence for patients with the last follow-up in 2024, the latest data was collected during the time of review.

DATA COLLECTION PROCEDURES:

Retrospective chart review from a prospectively maintained cohort of patients who underwent epilepsy surgery at the R Madhavan Nayar centre for comprehensive epilepsy care, Dept of neurology between 2000- 2023 was done. Screening to select the patients was done using the key search word hemispherotomy, functional hemispherectomy, motor cortex sparing hemispherectomy. Presurgical as well as post-surgical data along with functional outcome based on motor, cognitive and behavioral domains was collected including the information from the latest follow-up. Those patients satisfying the appropriate inclusion and exclusion criteria was included in the study. The seizure outcome was accessed using Engel score. The various variables that were studied as predictors of seizure outcome include demographic factors (age, sex, duration and type of epilepsy), etiology and pathological substrates, type of hemispherotomy, pre and post operative electroencephalography (EEG) parameters, imaging findings and postoperative complications.

DATA ANALYSIS:

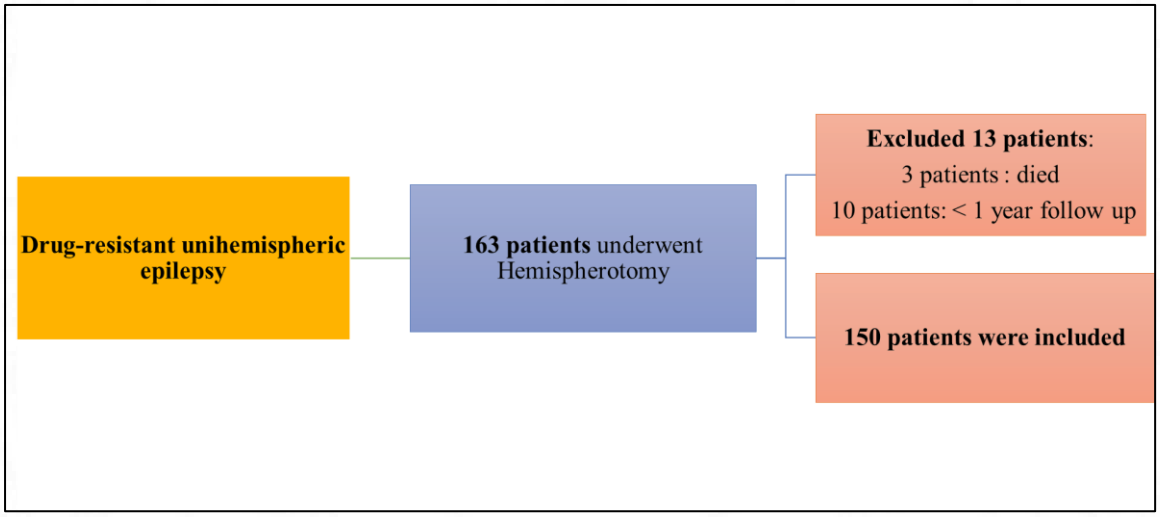
The data was analyzed with the help of computer software MS Excel and SPSS 21 for Windows. The data was presented as percentages or mean +/- standard deviation as defined appropriate for qualitative and quantitative variables respectively. Univariate analysis was undertaken to examine relationship of various factors. Crude odds ratio with 95% confidence interval was reported. Outcomes and its predictors was analyzed using Kaplan Meier curve, Mann Whitney U test, chi square test and Fisher exact test as appropriate. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome. A p value of <0.05 was considered statistically significant.

RESULTS

5. RESULTS

163 patients underwent hemispherotomy during the study period, among which three had died and 10 patients were excluded as they were lost to follow-up after a year (Figure 5.1). Among the total 150 patients enrolled, the mean age of seizure onset was **3.28±3.11** years, the age at surgery was 11.21 ± 6.39 years (range 9 months-38 years), the duration of epilepsy at surgery was 7.86 ± 6.15 years, the mean age at last follow-up was 16.79 ± 8.38 years and duration of follow-up post-surgery was **8.21 ± 5.01 years** (**range 1-24 years**). 105 patients (70%) were males and 89 patients (59.3%) were less than 12 years of age.

Figure 5.1: Selection of patients



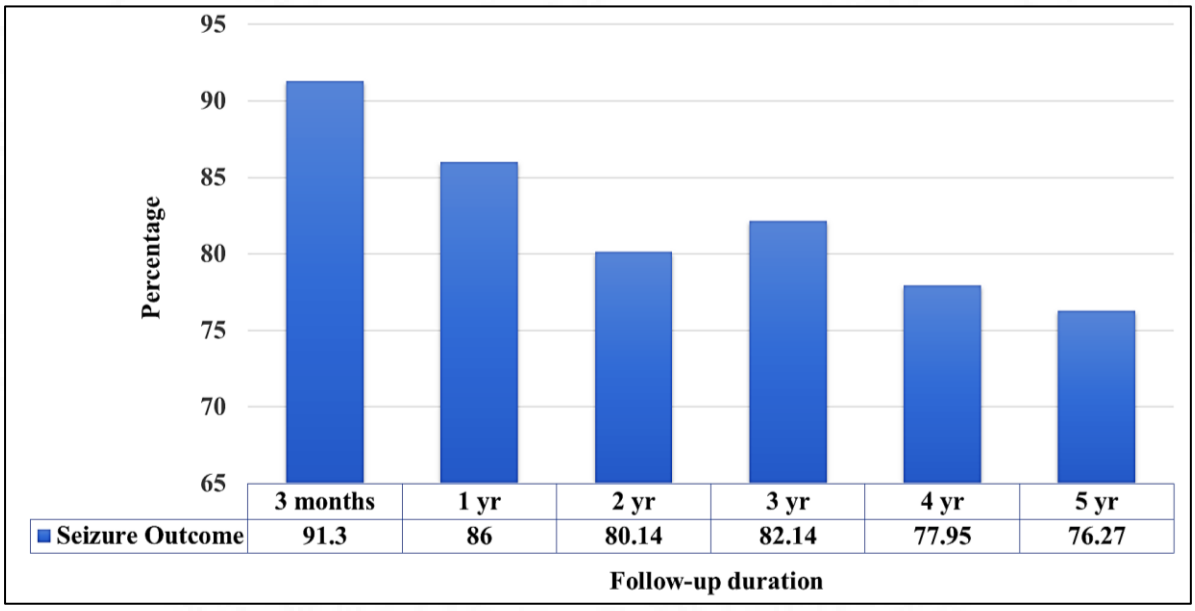
22 patients (14.7%) had preceding aura, and 72 (48%) had focal seizures with secondary generalization.112 patients (74.7%) were on polytherapy. The most common pathology was a porencephalic cyst (33 patients, 30%), followed by Rassmussen's encephalitis (23.3%). MRI showed contralateral pathology in 15 patients (10%). Interictal epileptiform discharges were lateralized only in 59 patients (39.3%) and ictal onset was ipsilateral in 66 patients (44%). 106

patients (70.7%) had slowing in the EEG with generalized slowing seen in 51 (34%). 145 patients (96.7%) underwent vertical parasagittal approach while the rest underwent a horizontal perisylvian approach. 32 patients (21.3%) had acute post-operative seizures (APOS).

SEIZURE OUTCOME

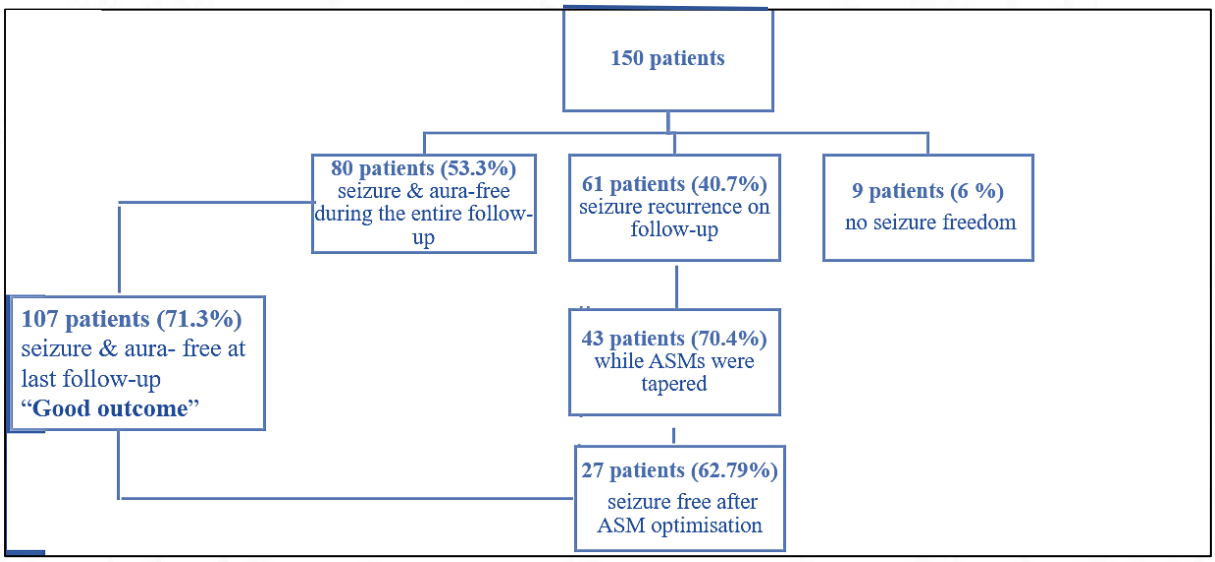
Engel class I outcome was seen in 137 patients (91.3%) at 3 months, 129 patients (86%) at 1 year, 117 patients (80.4%) at 2 year, 115 patients (82.14%) at 3 years, 99 patients (77.95%) at 4 years and 90 patients (76.27%) at 5 years follow-up (Figure 5.2).

Figure 5.2: Engel class I outcome in the first five years of follow-up



Among 61 patients who had seizure recurrence on follow-up, 43 patients (70.4%) had it while ASMs were tapered (Figure 5.3). However, at the last follow-up, 117 patients (78%) had Engel class I outcome, 107 (71.3%) were seizure-free (Engel Class I a), 37 patients (24.7%) were seizure-free and drug-free, and 108 patients (72%) had a reduction in the number of ASMs. 71.3% of patients with Engel Class Ia i.e. aura free and seizure free at the last follow-up were considered as the good outcome and were taken for further analysis.

Figure 5.3: Seizure outcome at the last follow-up



The pediatric group had 87.6% and adult age group had 83.6% patients with Engel class I outcome at 1 year follow-up (p-value:0.484) (Table 5.1). Even at 5-year follow-up, the seizure outcome was comparable between the pediatric and adult age group (77.3% vs 75%; p-value:0.783).

Table 5.1 Seizure outcome comparison between pediatric versus adult patients

Engel Class I outcome/Year of follow up	Pediatric (children <12 years)		Adults(≥12 years)		p-value
	N	%	N	%	
1 year	78	87.6	51	83.6	0.484
2 years	66	77.6	51	83.6	0.373
3 years	65	80.2	50	84.7	0.493
4 years	60	79.5	43	80.3	0.329
5 years	51	77.3	39	75	0.783
Last follow-up	70	78.7	47	77.0	0.841

PREDICTORS OF SEIZURE OUTCOME

71.3% of patients (n=107) with Engel Class Ia i.e. aura free and seizure-free at the last follow-up were considered as a good outcome and were taken for further analysis, rest of the patients were considered to have a bad outcome. Various clinico-demographic, EEG, imaging, and surgical parameters were compared among those who had good and bad seizure outcome to identify the predictive factors of surgical outcomes after hemispherotomy.

Clinico-demographic variables

Table 5.2 depicts the comparison of seizure outcomes between various clinical and demographic parameters. The mean age of onset of seizures, age at surgery, duration of epilepsy, and gender did not differ between the two groups. The presence of aura, secondary generalized seizures, frequency of seizures, or history of status epilepticus requiring ICU admission also was not found to affect the seizure outcome.

Table 5.2: Comparison of seizure outcome between various clinico-demographic paramaters

Parameter	Total	Seizure outcome		p-value
	N (%)	Good n = 107 (n, %)	Poor n=43 (n,%)	
Mean Age at onset, y (SD)	3.28 (±3.11)	3.30 (±2.85)	2.97 (±3.65)	0.560
Mean Age of surgery, y (SD)	11.21 (± 6.39)	11.02 (± 6.25)	11.59 (± 6.84)	0.623
Duration of epilepsy at surgery, y (SD)	7.86 (± 6.15)	7.72 (± 5.96)	8.62 (± 6.68)	0.422
Male Sex	105 (70)	78 (74.3)	27 (25.7)	0.222
Seizure characteristics				
Presence of Aura	22 (14.67)	17 (77.3)	5 (22.7)	0.505
Focal with bilateral tonic-clonic seizures	72 (48)	53 (73.6)	19 (26.4)	0.520
Polymorphic seizures	60 (40)	44 (73.3)	16 (26.7)	0.658
Daily seizures	121 (80.67)	90 (74.4)	31 (25.6)	0.092
Initial precipitating injury	95 (63.33)	50(52.63)	45 (47.36)	0.865
H/o Status epilepticus requiring ICU care	28 (18.67)	21 (75)	7 (25)	0.653

Pre-operative electroencephalography (EEG)

In the pre-operative EEG, the interictal data was lateralized in only 39.33% of patients. The ictal onset was lateralized in 44.67% of patients, and contralateral slowing was present in 34.67% of patients (Figure 5.4). However, none of the EEG variables were associated with seizure outcome (Table 5.3).

Figure 5.4: Pre-operative EEG variables

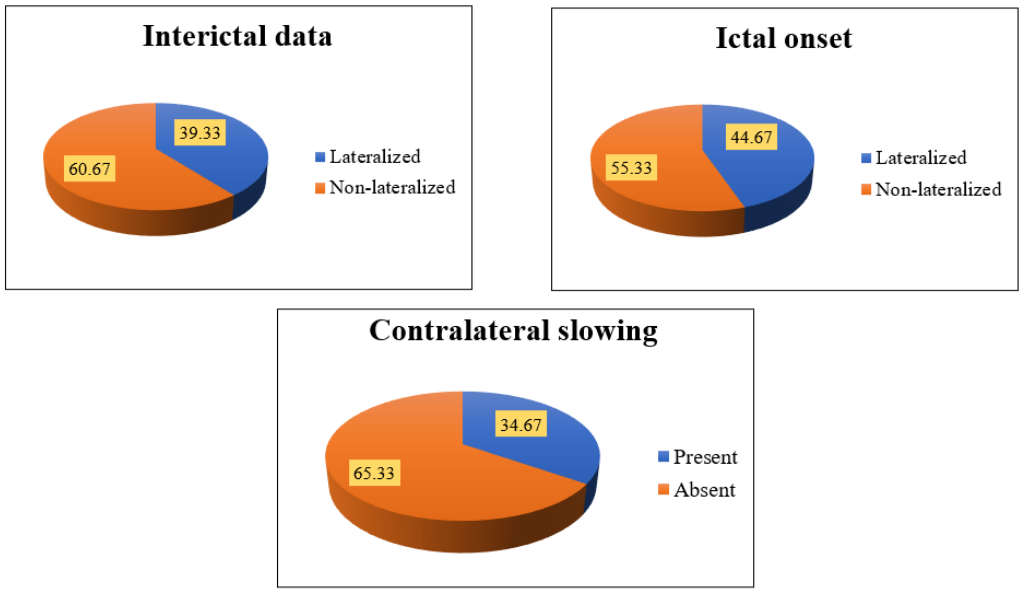


Table 5.3: Comparison of seizure outcome between various pre-operative EEG parameters

Parameter	Seizure Outcome		p-value
	Good , n = 107 (n, %)	Poor, n=43 (n,%)	
Interictal data Lateralized Non- Lateralized	 38 (64.4) 69 (75.8)	 21(35.6) 22(24.2)	0.131
Contralateral slowing	37 (75.6)	10 (24.4)	0.471
Ictal onset Lateralized	48 (71.6)	19 (28.4)	0.945

Etiology and imaging findings

The etiology was classified as developmental, acquired, and progressive. 59.33% of patients had acquired etiology, 26.7% had progressive and 18% had developmental anomalies. The most common being perinatal vascular insult. i.e. stroke (Figure 5.5) and the most common MRI abnormality was a porencephalic cyst (33 patients, 30%). Rassmussen's encephalitis was seen in 22.7% of patients. MRI showed contralateral pathology in 15 patients (10%). However, none of these variables were associated with seizure outcome (Table 5.4).

Figure 5.5: Classification of patients based on etiology

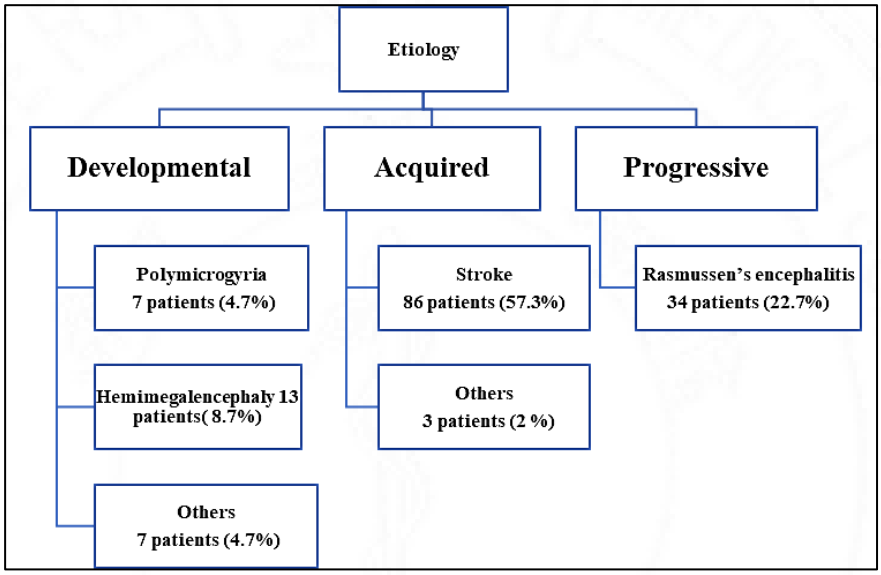


Table 5.4: Comparison of seizure outcome between various etiologies

Parameter	Total -n(%)	Seizure Outcome		p-value
	n(%)	Good , n = 107 (n, %)	Poor, n=43 (n,%)	
Etiology				
Developmental	27 (18)	17 (63)	10 (37)	0.364
Acquired	89 (59.33)	63 (70.8)	26 (29.2)	
Progressive	34 (26.67)	27 (79.4)	7 (20.6)	
Contralateral MRI features	15 (10)	11 (73.3)	4 (26.7)	0.857

Surgical techniques

The majority of patients (89.33%) underwent hemispherotomy, followed by 6.67% with functional hemispherectomy and 4% underwent anatomical hemispherectomy (Figure 5.6). 96.67% underwent vertical hemispherotomy while the rest of the patients under horizontal/ lateral parasylvian approach. But none of surgical variables as well as the prior resective surgery showed any association with seizure outcome (Table 5.5).

Figure 5.6: Classification of patients based on surgical techniques

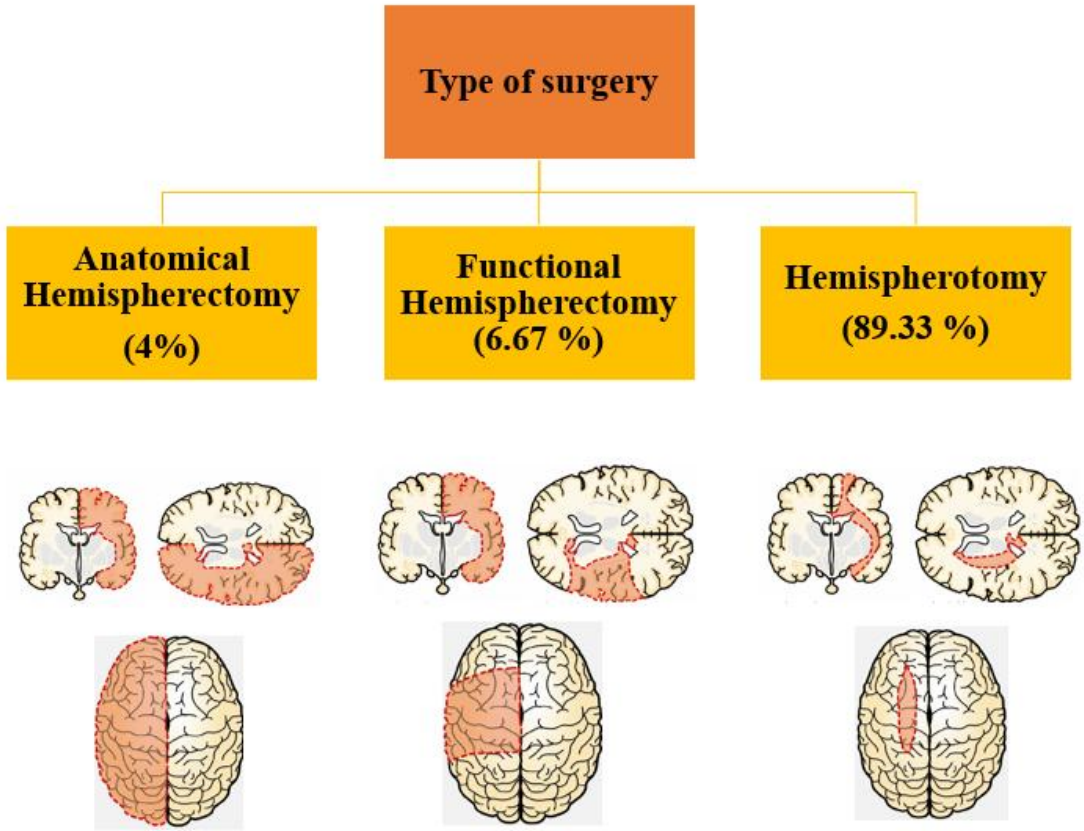


Table 5.5: Comparison of seizure outcome between various surgical techniques

Parameter	Seizure Outcome		p-value
	Good, n = 107 (n, %)	Poor, n=43 (n,%)	
Type of surgery			
Anatomical Hemispherectomy	5 (83.3)	1(16.7)	0.643
Functional Hemispherectomy	8 (80)	2 (20)	
Hemispherotomy	94 (70.1)	40 (29.9)	
Side of surgery			
Right	52 (76.5)	16 (23.5)	0.205
Left	55 (67.1)	27(32.9)	
Surgical approach- vertical	103 (71)	42 (29)	0.663
Prior resective surgery	5(50)	5(50)	0.123

Post-operative variables

Of all the variables analyzed by univariate analysis, the presence of acute post-operative seizures (APOS) (p-value 0.002), and the presence of contralateral slowing in post-operative EEG at one year (p-value 0.000) was associated with poor seizure outcome at the last follow-up (Table 5.6). As expected, the number of antiseizure medications was also significantly lower in patients with good seizure outcome.

Table 5.6: Comparison of seizure outcome between various post-operative variables

Parameter	Total	Seizure outcome		p-value
	N (%)	Good n = 107 (n, %)	Poor n=43 (n,%)	
Acute post-operative seizures (APOS) **Present** **Absent**	31 (20.67) 119 (79.33)	15 (48.4) 92 (77.3)	16 (51.6) 27 (22.7)	0.002
Post-operative EEG at 1 year				
Contralateral IEDs	45 (30)	36(80)	9 (20)	0.150
Generalized IEDs	3 (2.0)	37(77.1)	11 (22.9)	0.338
Contralateral slowing	36 (24.0)	13 (36.1)	23 (63.9)	0.000
Antiseizure medications (ASMs)				
Mean number of ASM pre-op, n (SD)	3.17 (±0.954)	3.14 (±0.956)	3.26 (± 0.954)	0.504
Mean number of ASM at last follow-up, n (SD)	1.79 (±1.45)	1.60 (± 1.08)	3.16 (± 1.07)	0.000
Contralateral slowing	36 (24.0)	13 (36.1)	23 (63.9)	0.000

Multivariate regression analysis

On multivariate logistic regression analysis, acute postoperative seizures (OR 3.08; 95% CI 1.23 to 7.69, p= 0.016) and the presence of contralateral slowing in post-operative EEG at one year (OR 7.64; 95% CI 3.25 – 17.97, p= 0.001) were independently predictive of poor seizure outcome (Table 5.7).

TABLE 5.7: Multivariate analysis for association between various variables and seizure outcome

Variables	P value	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Acute postoperative seizures (APOS)	0.016	3.08	1.23	7.69
Presence of contralateral slowing in post-operative EEG at one year	0.001	7.64	3.25	17.97

Survival analysis of longitudinal seizure outcome

Using Kaplan-Meier survival analysis, longitudinal seizure outcome curves were drawn for age at surgery and duration of epilepsy at time of surgery (Figure 5.7 and 5.8)

Figure 5.7: Kaplan-Meier survival curves illustrating seizure-free rates at various postoperative time intervals of paediatric vs adult age group

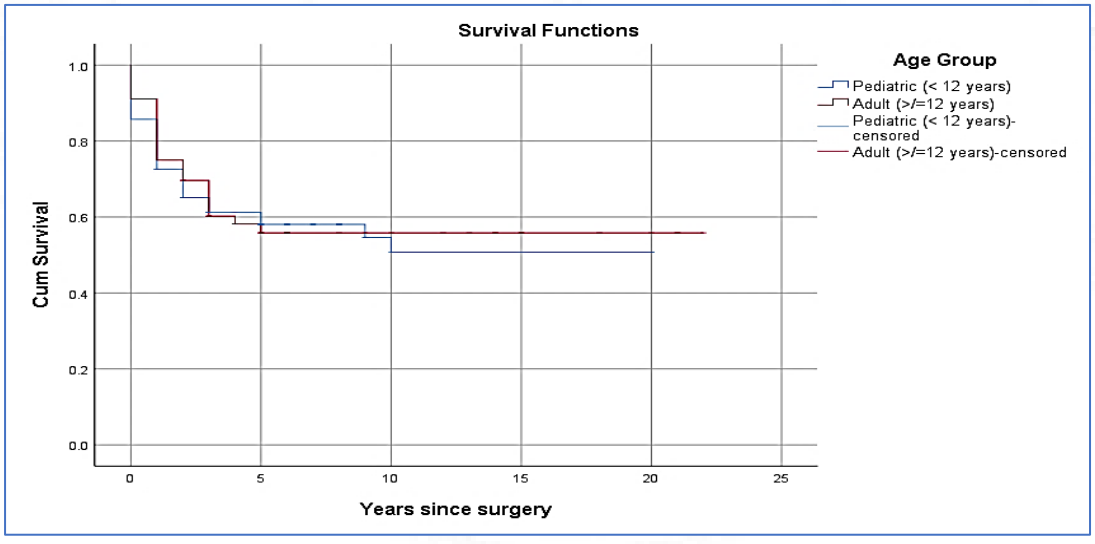
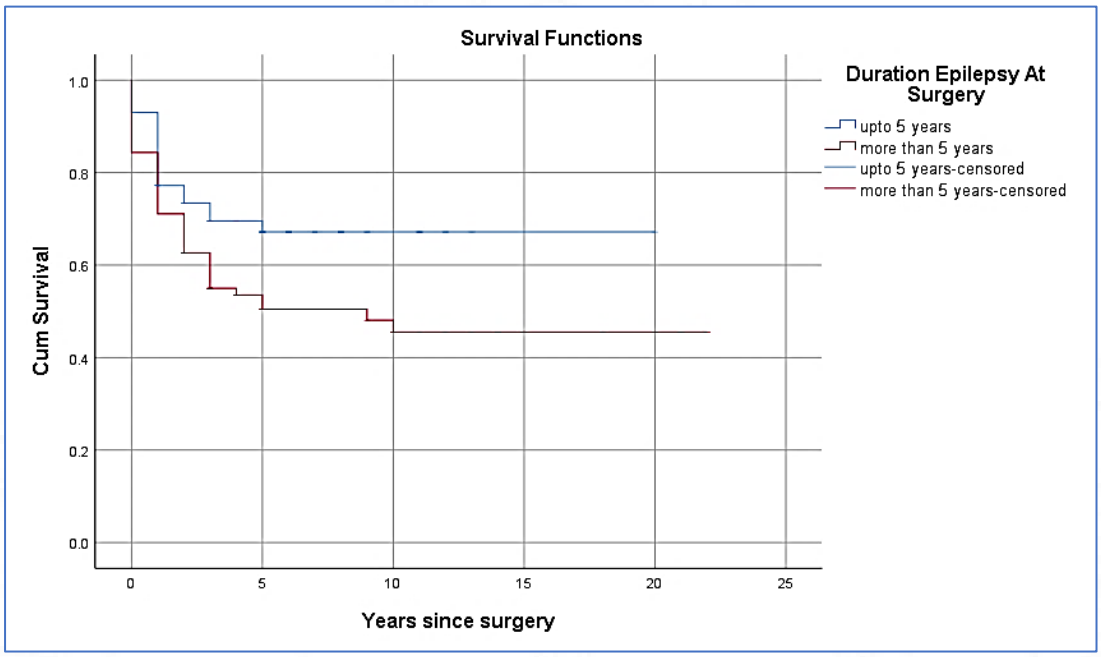


Figure 5.8: Kaplan-Meier survival curves illustrating seizure-free rates at various postoperative time intervals based on the duration of epilepsy at the time of surgery.



There was no significant difference in seizure freedom with regard to age at surgery(Figure 5.7). However, 68 % of patients with a shorter duration of epilepsy ($\leq$5 yrs) were seizure-free as compared to 44% of patients with a longer duration of epilepsy at the time of surgery, which was statistically significant (p-value 0.047).

FUNCTIONAL OUTCOME

At the last follow-up, 42% of patients had IQ $\geq$70. 86% had schooling, among them 50.39% started schooling post-surgery, 14 patients had high school education and 12 were college graduates. 31.3% of patients were employed, 12% (18 patients) were married, and 6.7% (10 patients) had children. 90% of patients achieved independent ambulation, 26% could grasp with hemiplegic hand, and 81.3% had improvement in language. Except for voluntary grasp(pediatric vs adult 41.6% vs 3.3%; p-value 0.00, and duration of epilepsy < 5 years vs > 5 years, 61.7% vs 2.2%; p-value 0.000), no significant difference was noted between other outcome variables and age or duration of epilepsy(p-value >0.05).

DISCUSSION

6. DISCUSSION

Hemispherotomy is considered as a safe and effective procedure for DRE associated with unilateral large epileptogenic lesion with contralateral neurological impairments, and if the preoperative evaluation confirms seizure onset in the lesioned hemisphere(4). However, given the rarity of the procedure, there is limited data on adult hemispherotomy, and no series with a comparison of the pediatric age group with the adult age group exists. In this study, we investigated the post-operative seizure outcomes of 150 eligible patients who underwent hemisphere resection and had postoperative follow-up of at least 1 year.

In our cohort, the estimated rate of seizure freedom with Engel class I outcome after hemispherotomy was 91.3% at 3 months, 86% at 1 year, 80.4% at 2 years, 82.14% at 3 years, 77.95% at 4 years and 76.27% at 5 years. Among 61 patients who had seizure recurrence on follow-up, 70.4% had it while ASMs were tapered. However, at the last follow-up, 117 patients (78%) had Engel class I outcome, 71.3% were seizure-free (Engel Class Ia), 24.7% were seizure-free and drug-free, and 72% had a reduction in the number of ASMs. Previously reported seizure freedom rates range from 65% to 80% from large series (5,6); however, two studies reported a decrease in seizure-free rates from 76% at 1 year to 58% at 5 years; and 76% at 1 year to 63% at 5 years (7,8).

On comparing pediatric age group and adults, we observed that the seizure outcome was comparable between two groups similar to prior studies (Table 6.1) on adult hemispherotomy series (5,9)However, data regarding long-term follow-up are scarce. As depicted in Table 6.1, the age cut-off employed in various studies also varied. We divided the age group based on the FDA pediatric age group of under 12 years and above (15). Eventhough we did not observe any difference in seizure outcome with regard to age at surgery, however, those with shorter epilepsy duration had the probability of having a better long-term seizure outcome. This emphasizes the need to bridge the surgical treatment gap by ensuring prompt referrals and addressing obstacles preventing epilepsy surgery.

Table 6.1: Comparison of adult and pediatric hemispherotomy series

Author, year	Age cut off	No: of patients	Follow-up	Class I Seizure outcome	Surgical technique
McClelland et al, 2007	>18 years	7	8 months- 36 years	55.6%	Hemispherectomy
Cukiert et al., 2009	>18 years	16	5.33 years	75%	Functional hemispherectomy
Schramm et al., 2012	>18 years	27	13 months- 19.5 years	81%	Functional hemispherectomy
Liang et al., 2013	>18 years	25	2 year - 6 years	92%	Anatomical or functional hemispherectomy
McGovern et al., 2019	> 16 years	47	5.3 years	77%	Functional ,modified anatomical and anatomical hemispherectomy
Bajaj et al., 2024	Pediatric <18years, adults ≥18 years	61 vs 11	12 months	88.9%	Hemispherotomy
Present study	Pediatric < 12years Adults ≥12 years	89 vs 61	8.21 years (range 1-23 years)	78%	Anatomical, functional hemispherectomy and hemispherotomy

On multivariate analysis, we identified two specific predictors of poor seizure outcome: APOS, and presence of contralateral slowing in post-operative EEG at one year. As noted in previous studies, we however did not find any correlation of seizure-free outcome with gender,

age at surgery, age of seizure onset, etiology, semiology, interictal EEG abnormalities, and bilateral MRI abnormalities(5,7).This information is crucial in a large volume center like ours to decide on the future selection of candidates for hemispherotomy.

Our data showed that there is an overall improvement in functional and social outcomes following hemispherotomy irrespective of age and duration at surgery except for hand function. While these findings highlight the significance of early surgery, they also demonstrate that older children may benefit significantly from this intervention. Knowledge regarding these socio-functional outcomes is crucial while counseling patients and families.

STRENGTH OF OUR STUDY

- The study had one of the largest cohort size of 150 patients from a single centre with a long follow-up duration ranging from 1 – 23 years.
- Ours is the first study to compare the outcomes between those who underwent surgery in the age group of up to 12 years and more than 12 years (i.e. pediatric vs older age group)
- We found that contralateral slowing in post-op EEG strongly predicts poor seizure outcome.

LIMITATIONS OF OUR STUDY

- As the consecutive DRE patients who underwent hemispherotomy from a single institution were enrolled, the results may be limited by referral bias.
- Comparison between individual hemispherotomy/hemispherectomy techniques was not done due to the smaller sample size in the subdivisions.

CONCLUSION

6. CONCLUSION

- Our study is one of the largest single-center experience on long-term outcome of hemispherotomy, and the first study to compare seizure outcome in pediatric age group and adults.
- The long-term seizure-free survival after hemispherotomy was 71.3% and 78% had Engel class I outcome at a mean follow-up of 8.21 years.
- The seizure outcome was comparable between pediatric and adults, however, the probability of seizure freedom based on survival analysis was significantly higher in patients with duration of epilepsy less than 5 years, suggesting that the earlier the surgery, the better!
- Acute post-operative seizures and the presence of contralateral slowing in post-operative EEG at one year were independent predictors of poor seizure outcome.
- There is an overall improvement in functional and social outcomes following hemispherotomy irrespective of age and duration at surgery except for hand function.
- Knowledge regarding these socio-functional outcomes is crucial while counseling patients and families.

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ANNEXURES

8. ANNEXURES

a. PROFORMA

SERIAL NO_____

AGE_____

SEX_____

AGE OF ONSET OF SEIZURES _____

AGE AT WHICH REFERRED FOR SURGERY_____

AGE AT EPILEPSY SURGERY _____

AGE AT LAST FOLLOW UP _____

DURATION OF LAST FOLLOW UP FROM SURGERY _____

DURATION OF EPILEPSY AT LAST FOLLOW UP _____

CLINICAL

1	TYPE OF EPILEPSY 1. FOCAL 2.GENERALISED 3. COMBINED	
2	ILAE classification of seizures	
3	Predominant type of seizures Focal seizures Generalised seizures Myoclonic Spasm Atonic Focal with secondary GTCS	1.Yes 2.No
4	Multiple types of seizures/polymorphic seizures Mention which all---------	1.Yes 2.No
5	Frequency of seizures in last 12 months Yearly Monthly Weekly Daily Specify the number also -----	
6	Neonatal convulsion	1.Yes 2.No
7	Febrile seizures	1.Yes 2.No
8	Status epilepticus	1.Yes 2. No
9	h/o status epilepticus requiring ICU care	1.Yes 2. No

10	h/o clustering of seizures	1. Yes 2. No
11	Presence of EPC	1.Yes 2. No
12	Presence of Infantile spasm	1.Yes 2. No
13	Perinatal insult If yes 1. Hypoxia 2. Hypoglycemia 3. Sepsis 4. Jaundice 5. Others ---mention	
14	Major Head trauma	1.Yes 2. No
15	Encephalitis	1.Yes 2. No
16	Neurological findings pre-op If yes, mention 1.Hemiparesis 2.UL = LL weakness 3. UL > LL weakness 4.LL > UL weakness 5.I/L Pincer weak 6. L/ Palmar grasp weak 7. Hemianopia 8. Aphasia 9.Dysarthria 10. any other deficits, mention ….	1.Yes 2. No
17	Pre-op mRS score	
18	Developmental delay	1.Yes 2.No
19	If yes 1. Global 2. Motor 3. Language 4. Social	
20	Cognition: IQ score DQ score	
21	Preop Speech assessment finding ----	
22	Behavioural issues present	1.Yes 2. No
23	Presence of Psychosis(as per DSMV)	1.Yes 2. No
24	Any behaviour modifying medcations	1.Yes 2. No
25	Number of ASM before surgery 1. Monotherapy 2. Dual therapy 3. Polytherapy 4. Exact number ……	
26	Name of ASMs	
27	Family h/o seizures	1.Yes 2.No
28	If any genetic testing done If yes report……	1.Yes 2. No

EEG

1	IEDs 1. Unilateral 2. Bilateral 3. Multifocal	
2	Location of maximum IED 1. Frontal 2. Parietal 3. Temporal 4. Occipital 5. Central 6. Combined	
3	IED: 1. Concordant – only one the affected side 2. Discordant- lateralised to opposite side 3. B/L independent 4. B/L symmetrical 5. Generalised	
4	Slowing 1.U/L 2. C/L 3. Generalised	
5	EEG seizures	1.Yes 2.No
6	If Yes : 1. Ipsilateral 2. Contralateral 3. Diffuse	
7	ESES Pattern	1.Yes 2.No
8	BA Pattern	1.Yes 2.No
9	Features of epileptic encephalopathy (disorganised BGA, lack of sleep structure on normal hemispshere, multifocal IED, BA)	1.Yes 2.No
10	Ictal onset 1. Unilateral 2. Contralateral 3. Diffuse 4. Not discernible	
11	Is ictal onset focal? If yes ictal onset region 1. Frontal 2. Parietal 3. Temporal 4. Occipital 5. Central 6. Combined	1.Yes 2.No
12	Ictal pattern 1. Unilateral slower rhythm (theta-delta) 2. Unilateral faster rhythm (alpha-beta) 3. Contralateral slower rhythm (theta-delta)	

	4. Contralateral faster rhythm (alpha-beta) 5. Diffuse onset with electrodecrement 6. Diffuse onset with slower theta -delta rhythm 7. Diffuse onset with faster alpha-beta rhythm	
13	Interictal EEG lateralization 1. Interictal lateralised 2. Interictal non-lateralised (bilateral or generalised)	
14	Ictal EEG lateralisation 1.Ictal lateralised 2.Ictal nonlateralized 3. Ictal contralateral	
15	Clinicoelectrical data concordant	1.Yes 2.No
16	Inter-ictal EEG concordant	1.Yes 2.No
17	Ictal EEG concordant	1.Yes 2.No

IMAGING

1	Type of MRI 1. 0.5T 2. 1.5T 3. 3 T	
2	Hemisphere involved 1. Unihemispheric 2. Bihemispheric	
3	Side 1.right 2. left 3.bilateral	
4	Ipsilateral hemisphere, MRI finding	
5	Is contralateral hemisphere involved in MRI If yes, the finding ……. • Cortical scars • Tuberous sclerosis, • Contralateral hemiatrophy in hemimegalencephaly, • Subependymal heterotopia, • Mild malformation of cortical development, • Polymicrogyria, and • Hippocampal sclerosis in the contralateral hemisphere • Periventricular leukomalacia • Wallerian degeneration • Delayed hemispheric myelination • Subcortical scar	1.Yes 2. No
6	Fmri	1.Yes 2.No
7	Finding of fMRI	If yes, 1-right, 2-left, 3-bilateral 4-uncertain
8	PET scan	1.Yes 2.No
9	Findings of PET	

	1. Ipsilateral 2. Contralateral 3. Bilateral 4. Normal	
10	Clinicoelectrical- radiological data concordant	1.Yes 2.No
11	WADA test	1.Yes 2.No
12	Findings of WADA	If yes, 1-right, 2-left, 3-bilateral 4-uncertain

ETIOLOGY

	Rasmussen's	
	Hemimegelencephaly	
	malformations of cortical development (MCD)	
	post-stroke	
	post-traumatic encephalomalacia	
	encephalopathy of unknown etiology	
	Sturge weber syndrome	
	Post encephalitic sequelae	
	Porencephalic cyst	
	HHE syndrome	
	Gliosis	
	Polymicrogyria	
	Pachygyria	
	Focal cortical dysplasia	
	Others -----	

HISTOPATHOLOGY

	Congenital	
	Acquired	
	Progressive	
	Mention the finding …….	

SURGERY

	Date of surgery	
	Year of surgery	
	Name of epilepsy surgery 1.Hemipsherotomy 2.Multilobar resection	
	If hemispherotomy a.Approach of surgery 1.Vertical 2. Lateral	
	b. Type of surgery 1.Anantomical Hemispherectomy 2. Functional hemispherectomy 3. Motor sparing hemispherectomy	

	4. Hemispherotomy	
	Side of surgery 1. Right 2. Left	
	Prior resective surgery done	1.Yes 2.No
	Complications 1.Significant blood loss 2.post op new onset hemiparesis 3. Acute post operative seizure(APOS) 4. SDH 5.Subdural collection 6. Hydrocephalus 7.Meningitis 8. any others, specify------	
	Any medical complication If yes, mention	1.Yes 2.No
	Complications : major vs minor (<3mth &>=3months) If major, mention-----	
	If APOS, which day after surgery	
	Post op day of discharge	
	Repeat surgery done	1.Yes 2.No
	If yes, reason for repeat surgery……	
	Persistent post op complications (>12yr) Duration :----- Mention the complication :	
	Died during study period: Age at time of death Duration from surgery Reason	

SEIZURE OUTCOME

	3month follow up Engel score (class): I. Free of disabling seizures II. Rare disabling seizures (almost seizure free) III. Worthwhile improvement IV. No worthwhile improvement	
	Engel outcome at each yearly follow up 1yr,2yr,3y,4yr,5yr,10yr,15yr,20yr,24yr	
	Last follow up after Surgery	Engel score
	Age at last follow up	
	year of last follow up	
	Time from surgery till last follow up (years)	
	Time to seizure recurrence (apart from APOS)	
	Post op seizure type: focal, generalised, combined,focal with secondary GTCS	
	Post op polymorphic seizures:	1. Yes 2. No
	Post op seizure type (ILAE classification)	
	Any new seizure type	1. Yes 2. No

	If yes..mention	
	No of ASM at 2 year follow up	
	No of ASM at last follow up	
	Reduction in ASM number : 1.Same 2.Decreased 3.Increased	
	Whether stopped ASM at last follow up	1.Yes 2.No
	Post op EEG : day 7 , 3 months, 1 year, 2 year, 5 year	
	Interictal EEG lateralization 1.Interictal lateralised (confined to side of lesion) 2. Interictal non-lateralised (independent c/l spike) 3. Generalised SWD	
	If post op seizures recorded If yes… 1.Ictal onset lateralised 2. Ictal onset contralateral 3. Ictal onset diffuse 4. ictal onset undiscernible	1.Yes 2.No
	Is post op MRI done : If yes, findings -----	1.Yes 2.No

FUNCTIONAL OUTCOME

	Functional outcome 1. Gross Motor : hemiparesis 2. Fine motor: a. pincer b palmar grasp 3. Language 4. Visual : a. Visual field b. perceived visual deficits 5. Cognition 6. Behaviour 7. Overall functional status	1. Unchanged 2. Improved 3. Declined
	Persistent weakness at last follow up	1. Yes 2. No
	Ambulant at last follow up	1. Yes 2. No
	Hand grip	1. Present 2. Absent
	Pincer grip	1. Present 2. Absent
	Going back to school	1.Yes 2. No
	Special schooling	1. Yes 2. No
	Employed	1.Yes 2. No
	If yes, details of job……	
	Married	1.Yes 2. No
	Children	1.Yes 2. No
	Pre and Post surgery	
	IQ DQ Speech	

b. IEC APPROVAL LETTER

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee

CDSCO Registration No: ECR/189/Inst/KL/2013/RR-21
DHR Registration No:ECINEW/INST/2022/2775

SCT/IEC/2234/JUNE/2024

29.07.2024

Dr. Nandana J
Post Doctoral Fellow
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Nandana,

The Institutional Ethics Committee held on 15th June, 2024, reviewed and discussed your application to conduct the study titled "**LONG TERM SURGICAL OUTCOME AND ITS PREDICTORS AFTER HEMISPHEROTOMY AND MULTILOBAR RESECTION FOR DRUG RESISTANT EPILEPSY (IEC /2234)**"

Principal Investigator	Dr Nandana J, R MadhavanNayar centre for comprehensive epilepsy care, Department of Neurology, SCTIMST
Co-Principal Investigator(s)	Dr Ashalatha Radhakrishnan, Department of Neurology, SCTIMST Dr K Y Manolia, Department of Neurology, SCTIMST Dr Rumshekhar N Menon, Department of Neurology, SCTIMST Dr George C Vilanilam, Department of Neurosurgery, SCTIMST Dr Bejoy Thomas, Department of Imaging Sciences and Interventional Radiology, SCTIMST Dr Kesavadas C, Department of Imaging Sciences and Interventional Radiology, SCTIMST
Duration of the study	4 months

The following members of the Ethics Committee were present at the meeting held on 15th June, 2024

Sl. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kusuma Kumary P	M.D in Paediatrics	Female	Clinician (Chairperson)	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Dr. Annapurna Y	MD	Female	Basic Medical Scientist	No
4.	Dr. Indu PV	MBBS, DPM, MPhil, PhD	Female	Clinician	No
5.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
6.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
7.	Smt. Rekha Radhakrishnan	M.A (Eng.); B.Ed	Female	Lay person	No
8.	Dr. Harikrishna Varma PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
9.	Dr. Manikandan S	MBBS,MD,PDCC	Male	Clinician	Yes
10.	Dr. Narayanan Namboodiri. K.K	MBBS,MD,DM	Male	Clinician	Yes
11.	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
12.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Checklist Form
2. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 22.04.2024
3. Covering letter addressed to the Chairperson, IEC, SCTIMST dated20.04.2024 from Dr. Ashalatha, Professor, Department of Neurology, SCTIMST
4. IEC Application Form
5. Declaration Form
6. Research Proposal
7. CV of PI and Co-PIs
8. Proforma
9. SRC Recommendation Letter

Revised submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 17.07.2024
2. Response to IEC Recommendations
3. Checklist Form
4. Covering letter addressed to the Chairperson, IEC, SCTIMST Forwarded by HOD, Department of Neurology, SCTIMST
5. Covering letter addressed to the Chairperson, IEC, SCTIMST dated20.04.2024 from Dr. Ashalatha, Professor, Department of Neurology, SCTIMST
6. IEC Application Form
7. Declaration Form
8. Research Proposal
9. CV of PI and Co-PIs
10. Proforma

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. Syam. K
Alternate Member Secretary, IEC



Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **6.5%**

Date: Dec 26, 2024

Statistics: 445 words Plagiarized / 6852 Total words

Remarks: Low similarity detected, check your supervisor if changes are required.