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Islam Magdy Ali Ibrahim

Neurosurgery Department Faculty of Medicine, Al-Azhar University Cairo , Egypt, imagdy212@gmail.com

Mamoun abo shosha

Neurosurgery Department Faculty of Medicine, Al-Azhar University Cairo , Egypt

Mohamed Meligy Rabea Hamed

Neurosurgery Department Faculty of Medicine, Al-Azhar University Cairo , Egypt

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ORIGINAL ARTICLE

Clinical Outcome of Corpus Callosotomy for Management of Drug Resistant Epilepsy

Islam Magdy Ali Ibrahim^{a,*}, Maomon Mohamed Abo Shosha^a,
Mohaed Meligy Rabea Hamed^b

^a Department of Neurosurgery, Faculty of Medicine, Al-Azhar University, Egypt

^b Department of Neurosurgery, Faculty of Medicine, Al-Azhar Assiut University, Egypt

Abstract

Background: One of most common chronic neurologic disorders is epilepsy, incapability of significantly reduce percentage of studied cases resistant to all available antiepileptic treatments without producing unacceptable side effects is particularly frustrating.

Aim: Aim of the research was to investigate seizure result following corpus callosotomy in relation to extent of resection in pediatric studied cases with Symptomatic generalized epilepsy with normal preoperative brain imaging on MRI Brain.

Patients and methods: Research entails prospective analysis of data from 20 pediatric patients who were treated for intractable symptomatic generalized epilepsy by corpus callosotomy.

Results: In the patient series, 13 patient suffered from generalized tonic clonic fits (56.3%) and 7 patient is multi focal fits (43.8%) one of them is Lennox gustate syndrome, no statistically significant variation (P value = 0.101) among grade II and grade III studied cases as regard presentation.

Conclusion: Corpus callosotomy affords a good outcome for drop attacks, at least 70% of patients will experience free from these attacks, a so it will abolish the harmful effects like bodily injury, limited activity and caregivers' dependency. In pediatric studied cases, there is no variation in result among total and anterior 2/3 colostomy except some cases may complicate in total colostomy with disconnection syndrome, but anyway these cases show better improvement than adult cases.

Keywords: Corpus callosotomy, Drug resistant epilepsy, Management

1. Introduction

Epilepsy is one of most prevalent chronic neurologic disorders, incapability of significantly reduce percentage of studied cases resistant to all available antiepileptic medications without producing unacceptable side effects is particularly frustrating.¹

Surgical resection of anatomic location responsible for seizures is one of options available to this group of studied cases. Despite fact that surgical results are significantly better than published likelihood of pharmacologic success after 2 to 3 antiepileptic drugs fail to produce seizure control, significant hesitancy precedes start of surgical assessment. Apprehension is especially strong in

pediatric population, where determinants of surgical results are poorly documented.²

Recent studies show that surgery is beneficial in 56%–100% of studied cases, with more than fifty percent advancement in frequency of generalized seizures.³

Corpus Callosum may act like modulator of cortical activity, transmitting both inhibitory and excitatory influences. As result, cortex can produce inhibitory and excitatory activity, which is balanced by Corpus Callosum. Axons in corpus callosum connect most areas of cerebral cortex to homologous areas in opposite hemisphere.⁴

Van Wagenen and Herren first used corpus callosotomy as palliative therapy for intractable seizures in 1940. Modified surgical methods have been

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* Corresponding author. Alsharkia Governorate, Alhussaynia, Egypt.
E-mail address: imagdy212@gmail.com (I.M.A. Ibrahim).

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investigated since 1970s. Anterior frontal inter-hemispheric approach for staged callosotomy, anterior callosotomy, and, more recently, radio-surgical callosotomy with gamma knife are some of these methods.⁵

Corpus callosotomy is palliative surgical procedure for studied cases who, despite having intractable seizures, are not candidates for focal resistive surgery. Drop attacks (tonic and atonic seizures) and also tonic-clonic, absence, and frontal lobe complex partial seizures are best treated with corpus callosotomy (CC).⁶

Rationale for corpus callosotomy is based on hypothesis that CC is most effective route for inter-hemispheric spread of epileptic activity. Ictal activity spread is hampered when connections among hemispheres are severed. Furthermore, if neurons in both hemispheres are needed for seizure generation in some circumstances, seizure frequency may be reduced.⁷

Number of factors must be considered when evaluating studied cases for possible callosotomy. Medical intractability must be demonstrated by failure of multiple treatments, and seizures should typically be of type that can cause bodily harm from falls. Effect of seizures on studied case's life should be evaluated, as well as impact of seizures on family and caregivers.⁸

Callosotomy is curative, and seizures usually persist to some extent after operation. Before operation, it is necessary to consider how potential decrease in seizure frequency or intensity, or removal of certain seizure types, would affect studied cases and family. Studied cases and family's goals and expectations, and uncertainties, should be discussed.⁹

Extent of corpus callosum resection, risk of complications, and studied case selection remain contentious. Numerous transient and some permanent sequelae, such as hemiparesis, apraxia, and mutism, may also happen. Although some symptoms are caused by disruption of corpus callosum, others are caused by surgical procedure itself. Modification of operative method may reduce frequency and possibly severity of these problems.¹⁰

Aim of research was to investigate seizure result following corpus callosotomy in relation to extent of resection in pediatric studied cases with Symptomatic generalized epilepsy with normal preoperative brain imaging on MRI Brain.

2. Patients and methods

Research entails prospective analysis of data from 20 pediatric patients who were treated for intractable symptomatic generalized epilepsy by corpus callosotomy.

2.1. Inclusion criteria

Seizure semiology (generalized epileptic seizures proved by video EEG), normal MRI brain, generalized interictal pattern with or without bilateral synchronization, generalized ictal discharges without any focal predominance and patient with general epilepsy due to lesion cannot be excised.

2.2. Exclusion criteria

Focal pathology on MRI correlated with the EEG finding, lateralized interictal epileptiform discharge, temporal lobe epilepsy, patient with bad general condition and patient with comorbidities.

2.3. Patients

20 patients were diagnosed by the Epileptology multidisciplinary team at ALAZHAR University Hospitals as suffering from intractable symptomatic generalized epilepsy with normal MRI or MRI show lesion not excisable were enrolled in this study.

2.4. Methodology

2.4.1. Presurgical evaluation

Studied cases are subjected to following protocol.

2.4.2. Detailed history from parents, including

Years old of seizure onset, time of epilepsy, seizure semiology, a history of treatment including type of antiepileptic drugs including: Proper drug choice, check the presence of faulty combinations, proper dosing and dosing frequency according to the age, sex, body weight and the nature of seizures, assessment of the side effects with AEDs and drug resistant epilepsy is described as failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drug schedules to accomplish sustained seizure freedom over period of 12 months and history of other lines of treatments.

2.4.3. Clinical assessment

Clinical evaluation entailed full neurological examination.

2.4.4. Electrophysiological

Prolonged video-EEG was done using scalp electrodes to record ictal and interictal abnormalities throughout wakefulness and sleep in studied cases receiving standard and decreased AED dosages. Interictal EEG showed a generalized pattern, whether bilaterally synchronized or not (varieties will be discussed in the results). Ictal EEG showed

diffuse generalized pattern without focal predominance.

2.4.5. Neuroimaging

Routine 3-T MRI brain in multi-sequences, all the patients included in this study had normal MRI brain without structural lesion. SISCOM analysis was done in all cases in a trial to find any focal abnormality. All cases showed unremarkable finding.

2.4.6. Surgical treatment: surgical technique

All patients were generally anesthetized, supine position with flexed head fixed in May field, right frontal paramedian approach for all the patients. The neuronavigator were used to estimate the end point for anterior two third callosotomy accurately where it was located 4.5–5.5 cm from the genu in all cases. While in total callosotomy cases, certainty intraoperative were achieved by seeing the vein of Galen.

2.4.7. Postoperative care

After surgery, patients were routinely monitored in ICU for 2 days, and then transferred to a regular room for one week unless complications were occurring and needed a special care.

2.4.8. Postoperative radiology protocol

24 h postoperative, regular Computed tomography (CT) brain was obtained as a routine postoperative follow-up. Before discharge 3-T MRI brain was done to document the extent of corpus colostomy.

2.4.9. Follow-up

All the patients underwent regular monthly follow-up at the outpatient clinic under the supervision of pediatric neurologist and the surgeon, follow-up include: Clinical assessment: Neurological examination and type of seizure, electro-physiological by interictal EEG, studied cases were kept on antiepileptic drugs throughout the follow-up period and seizure frequency every 1 month was monitored. The main 3 items of our study: Seizure outcome: Following surgery, studied cases were classified as follows: class 1, seizure free; class 2, rare seizures (>90% decrease); class 3, 75–90% decrease in seizures; class IV, seventy five percent decrease in seizures; and class V, seizure worsening. Studied cases underwent EEG throughout follow-up to evaluate seizure advancement & recurrence. Antiepileptic drug: Antiepileptic drugs were maintained at their preoperative dosage and schedule for 3 months postoperative, after those changes were made if deemed appropriate by a pediatric neurologist.

2.5. Statistical analysis

Statistical Program for Social Science version 24 was used to analyses data. Quantitative data were presented as mean \pm SD. Frequency and percentage of qualitative data were used. Mean (average): sum of values divided by number of values; central value of discrete set of numbers. Standard deviation: is measure of spread of set of values. Low SD shows that values are close to set's mean, whereas high SD shows that values are spread out over wider range.

3. Results

20 patients were involved in this study and all diagnosed as interactable fits and undergo corpus callosotomy (Table 1).

This table shows the description of demographic data in cases. As regard age, mean years old of studied cases was 12.3 ± 8.4 years with minimum years old of 4 years and maximum years old of 40 years. As regard sex, there were 12 men (60%) and 8 women (40%) in studied cases (Table 2).

This table founds description of clinical data in all studied cases. As regard mentality, it was normal in 13 patients (65%) and subnormal in 7 patients (35%) of the studied patients. As regard clinical presentation, it was generalized tonic clonic seizures in thirteen studied cases (65%) and multi-form seizures in 7 patients (35%) of studied cases. As regard epilepsy duration, mean duration of studied cases was 5.5 ± 2.8 years with minimum duration of 2 years and maximum duration of 11 years (Table 3).

This table describes description of MRI brain findings in all studied cases. MRI brain revealed mild brain atrophy in 7 patients (35%) while it was NAD in 13 patients (65%) of the studied patients (Table 4).

This table describes description of postoperative problems in all studied cases. Postoperative complication has been occurred in 4 patients (20%) of the studied patients. 1 patient developed 1 month behavior change, 1 patient had left lower limb weakness with power, 1 patient had left side focal fits for second in second day and 1 patient died due to chest infection after 15 of operation (Table 5).

Table 1. Description of demographic data in all cases.

	Studied patients (N = twenty)	
Sex		
Men	Twelve	Sixty percent
Women	Eight	Forty percent
Years old		
Mean \pm SD	12.3 ± 8.4	
Min - Max	4–40	

Table 2. Description of clinical data in all studied cases.

	Studied patients (N = 20)	
Mentality		
Normal	13	65%
Subnormal	7	35%
Presentation		
Generalized tonic clonic seizures	13	65%
Multi-form seizures	7	35%
Epilepsy duration (years)		
Mean \pm SD	5.5 \pm 2.8	
Min – Max	2–11	

Table 3. Description of MRI brain findings in studied cases.

	Studied cases (N = 20)	
MRI brain		
NAD	13	65%
Mild brain atrophy	7	35%

Table 4. Description of post-operative problems in studied cases.

	Studied patients (N = 20)	
Postoperative complications		
No	16	80%
Yes	4	20%

Table 5. Description of outcome (ENGEL classification) in studied cases.

	Studied patients (N = 20)	
Outcome (ENGEL classification)		
Grade II	16	80%
Grade III	4	20%

This table describes description of outcome (ENGEL classification) in all studied cases. It was grade 2 in 16 studied cases (80%) and grade 3 in 4 studied cases (20%) (Table 6).

There was no statistical important variation (P -value = 0.080) among grade II and grade III studied cases as regard years old. It was 11.2 ± 8.2 years in grade II patients and 16.7 ± 8.5 years in grade III patients. No statistically significant variation (P -value = 0.648) among grade II and grade III studied

cases as regard sex. There were 10 males (62.5%) and 6 females (37.5%) in grade II patients while there were 2 men (50%) and 2 women (50%) in grade III studied cases (Table 7).

There was no statistical important variation (P -value = 0.101) among grade II & grade III studied cases as regard mentality. There were 9 normal patients (56.3%) and 7 subnormal patients (43.8%) in grade II patients while all grade III patients (100%) were of normal mentality. No statistically significant variation (P -value = 0.101) among grade II and grade III studied cases as regard presentation. There were 9 generalized tonic clonic seizures patients (56.3%) and 7 Multi-form seizures patients (43.8%) in grade II patients while all grade III patients (100%) were of Generalized tonic clonic seizures. Statistically important (P -value = 0.001) decreased duration in grade II patients (4.4 ± 1.9 years) when compared with grade III patients (9.8 ± 1.3 years) (Table 8).

There was no statistical important variation (P -value = 0.639) among grade II & grade III studied cases as regard brain MRI. There were 6 patients (37.5%) with mild brain atrophy in grade II patients while there was 1 patient (25%) with mild brain atrophy in grade III patients. No statistical important variation (P -value = 0.094) among grade II and grade III studied cases as regard postoperative problems. There were two studied cases (12.5%) with postoperative complications in grade II patients while there was 2 patients (12.5%) with postoperative problems in grade III studied cases.

3.1. Case number (1)

Women studied cases, 10 years old, with mild subnormal mentality, introduced with 4-year history of recurrent attacks of multiform seizures (containing generalized tonic seizures, atonic seizures, and automatism) that were not well managed to use of multiple antiepileptic treatments that reached up to 5 drugs (sodium valproate, clonazepam, levetiracetam,

Table 6. Relation between outcome and demographic data.

	Outcome		Stat. exam	P-value
	Grade 2 (N = sixteen)	Grade 3 (N = four)		
Years old				
Mean \pm SD	11.2 \pm 8.2	16.7 \pm 8.5	MW = 13	0.080 NS
Sex				
Male	10	62.5%	2	50%
Female	6	37.5%	2	50%

MW, Mann Whitney U test.

χ^2 : Chi-square exam.

NS: P -value >0.05 is considered nonsignificant.

Table 7. Relation between outcome and clinical data.

	Outcome		Stat. test	P-value
	Grade 2 (N = sixteen)	Grade 3 (N = four)		
Mentality				
Normal	9	56.3%	$\chi^2 = 2.6$	0.101 NS
Subnormal	7	43.8%		
Presentation				
Generalized tonic clonic seizures	9	56.3%	$\chi^2 = 2.6$	0.101 NS
Multi-form seizures	7	43.8%		
Duration (years)				
Mean \pm SD	4.4 \pm 1.9	9.8 \pm 1.3	MW = 1.0	0.001 S

MW, Mann Whitney *U* exam.

S: P-value <0.05 is considered significant.

χ^2 : Chi-square exam.

NS: P-value >0.05 is considered nonsignificant.

eslicarbazepine, and topiramate) despite adequate treatments seizures advanced and became resistant to medical therapy. She had two and three attacks per day that disrupted her life.

Preoperative brain imaging (Fig. 1) indicated mild brain atrophy with no other structural brain lesions, as well as bi-frontal epileptic activity on electroencephalography.

Studied case underwent microscopic anterior corpus callosotomy with no intra or postoperative problems, and he did not have any seizures in early postoperative period.

Following-up after 1 month, brain MRI was performed to assess extent of callosotomy, as seen in Fig. 2.

Studied case was followed for 36 months, and seizures improved to class II (Engel classification). After 12 months, antiepileptic medication withdrawal was initiated, and studied case was reduced to using only two treatments with good epilepsy control.

3.2. Case number (2)

Men studied cases, 29 years old, with normal mental status, introduced with history of recurrent attacks of generalized tonic-clonic seizures for 20

years and not being controlled at all during this time despite using various anti-epileptic treatments that were adequate and in adequate doses. Antiepileptic treatments could be taken at same time (Sodium Valproate, Levetiracetam, and Carbamazepine).

Seizures progressed and became resistant to medical therapy. An 18 years-old studied case had severe seizure attack that included fall from great height and head trauma, resulting in intracranial hemorrhage that necessitated surgical evacuation to other hospitals.

Preoperative brain imaging (Fig. 3) discovered mild brain atrophy with right fronto-parietal encephalomalacia, which was caused by previous head trauma and surgical evacuation of intracranial hemorrhage.

Repeated interictal electroencephalograms revealed bilateral fronto-temporal foci of epileptic activity (Fig. 4).

Without any intra-operative problems, studied case underwent microscopic anterior corpus callosotomy. He experienced postoperative nonsignificant transient problem in form of left sided focal fits lasting seconds on second day only.

On second postoperative day, brain Computed tomography (CT) was performed to assess and

Table 8. Relation between outcome and (brain MRI and postoperative complications).

	Outcome		Stat. test	P-value
	Grade 2 (N = sixteen)	Grade 3 (N = four)		
Brain MRI				
NAD	10	62.5%	$\chi^2 = 0.22$	0.639 NS
Mild brain atrophy	6	37.5%		
PO complications				
No	14	87.5%	$\chi^2 = 2.8$	0.094 NS
Yes	2	12.5%		

MW, Mann Whitney *U* tests.

χ^2 : Chi-square exam.

NS: P-value >0.05 is considered non-significant.

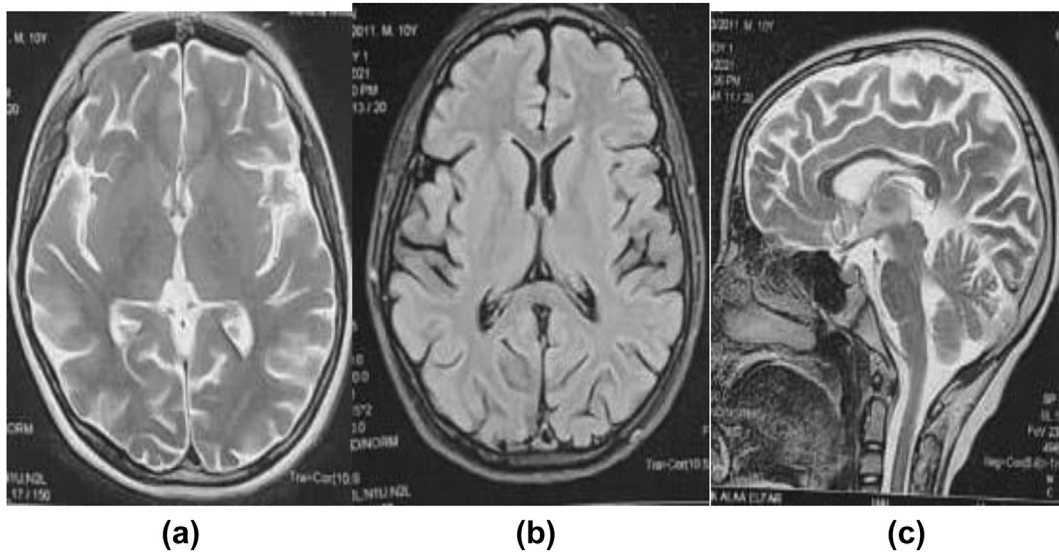


Fig. 1. Brain MRI images. (a) T2 axial cut, (b) FLAIR axial cut, (c) T2 mid-sagittal cut which revealed mild brain atrophy with no structural lesions and normal corpus callo-sum.

search for reason for focal fits, as well as to assess extension of callosotomy, as shown in Fig. 5.

Studied case was followed for 33 months and seizures improved to class III (Engel classification). After 12 months, antiepileptic treatment withdrawal was initiated, and studied case was reduced to only two treatments with good epilepsy control.

4. Discussion

Generalized epilepsy may be idiopathic or symptomatic; the idiopathic type is a benign type

and rarely become intractable and even though, this intractability could be treated with medical treatment after proper investigations and management. While symptomatic type is a difficult entity mostly suffering from intractability with a lot of trials to manage it Seneviratne and colleagues.¹¹

Some reports published that preoperative intracranial monitoring for such like cases may reveal undiscovered epileptic focus and subsequent resection of this focus may result in better outcomes Chen and colleagues.¹²

Other reports published that corpus callosotomy may lead to lateralization of the ictal EEG finding and help in discovering respectable focus and its resection lead to the improvement of the seizure outcome Ono and colleagues.¹³

In our patient series, 13 patient suffered from generalized tonic clonic fits (56.3%) and 7 patient is multi focal fits (43.8%) one of them is Lennox gus-tate syndrome, No statistical important variation (P -value = 0.101) among grade II & grade III studied cases as regard presentation.

In our series no studied case suffered from worsening in seizure frequency and severity. This is correlated with other published reports as we did not find any published series reported worsening of seizure after callosotomy Silverberg and colleagues.¹⁴

According to the neurodevelopmental outcome, patients with seizure free showed marvelous improvement in their daily activities, less family dependence and IQ improvement. Even though, a lot of reports indicate the explanation may be



Fig. 2. Brain MRI T1 mid-sagittal cut revealing good extension of cut of ante-rrior two thirds of corpus callosum.

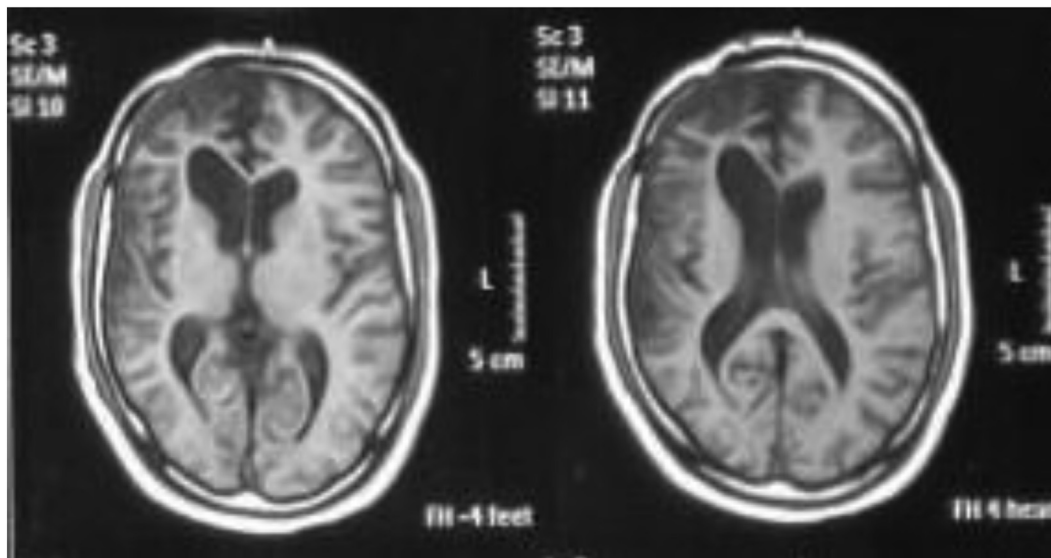


Fig. 3. Brain MRI T1 axial cuts viewing mild brain atrophy with right fronto-parietal mild encephalomalacia and overlying previous flap of surgery of hemorrhage evacuation.

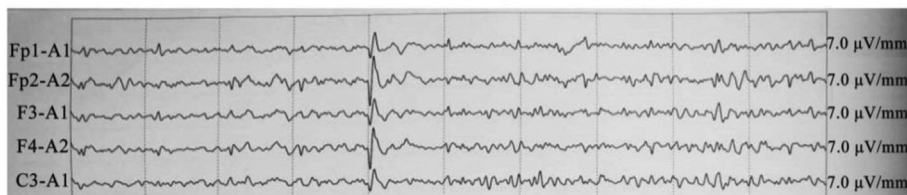


Fig. 4. Capture photo taken from studied case EEG revealing bilateral focal fronto-temporal epileptiform activity in form of spikes and slow waves complexes more on right side.

directed toward the disappearance of disabling factors, less use of antiepileptic drugs and avoidance of their harmful effects. Also, the family and community play a role in this as with improvement in

seizure outcome; the patient becomes more comfortable with the surroundings and has a little restriction from the family toward his activities Paul and colleagues.¹⁵

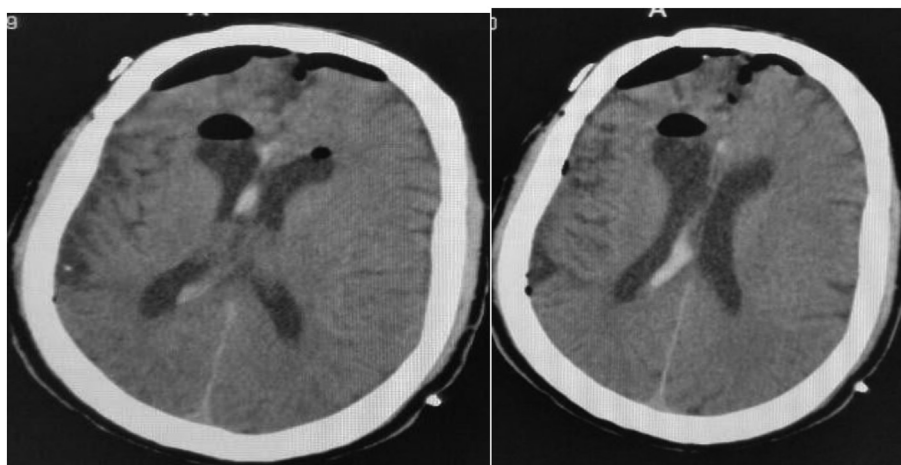


Fig. 5. Brain Computed tomography (CT) axial cuts which exposed expected good extension of cut of corpus callosum and there was minor intraventricular bleeding and minor pneumocephalus.

Gillam et al. in his postoperative follow-up applied a study for developmental improvement in children; he found a good outcome with no relation to seizure outcome but with significant relation to a suppressed bilateral synchronization Yonekawa and colleagues.¹⁶

In our serious studies postoperative complications were seen in 4 cases (20%) one patient develop focal fits, one patient develop chest infection and die on top of that, one patient develop weakness and one patient develop behavior change but no significant relation between the surgery and complication (P value = 0.094), and this considered low out come in comparison with the previous publications reported a significant relation between the total callosotomy and disconnection syndrome, but a few series reported that disconnection syndrome is not highly found in children below the age of 6 after doing total callosotomy as a one stage procedure or after second surgery for splenium. There is no evidenced based explanation for these findings, but some correlated it with plasticity of the CNS which is more apparent in posttraumatic cases during childhood period Ramey and colleagues.¹⁷

On the other hand, all reports considered anterior 2/3 callosotomy are safer without any major neurological complications and that makes a lot of centers preferring this procedure as an initial stage could be completed later if no improvement occurs to seizure outcome Truong and colleagues.¹⁸

In our patients, all the radiological investigations failed to localize a discharge focus. Other publications reported that the normal MRI is associated with better outcome, but these studies had a lot of abnormal finding on MRI of patients with bad outcomes Asadi-Pooya and colleagues.¹⁹ Although there are quite enough publications about callosotomy but, no specific criteria established as a predictor of outcome. Some authors in recent studies correlate better outcome with normal MRI, early surgical intervention, and an absence of mental retardation. On the other hand another series reported that these factors may play a role but failed to reach a significant value Arya and colleagues.²⁰

In our study found highly significant value among time of epilepsy and result of corpus callosotomy statistically significant (P value = 0.001) decreased duration in grade II patients (4.4 ± 1.9 years) when compared with grade III patients (9.8 ± 1.3 years).

4.1. Conclusion

Corpus callosotomy affords a good outcome for drop attacks, at least 70% of patients will experience

free from these attacks, a so it will abolish the harmful effects like bodily injury, limited activity and caregivers' dependency. In pediatric studied cases, there is no variation in result among total and anterior 2/3 colostomy except some cases may complicate in total colostomy with disconnection syndrome, but anyway these cases show better improvement than adult cases.

Consent for publication

I verify that all authors have approved to submit manuscript.

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The authors declared that there were NO conflicts of Interest.

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