Endoscopic-Assisted (Through a Mini Craniotomy) Corpus Callosotomy Combined With Anterior, Hippocampal, and Posterior Commissurotomy in Lennox-Gastaut Syndrome: A Pilot Study to Establish Its Safety and Efficacy

BACKGROUND: Corpus callosotomy is a palliative procedure especially for Lennox-Gastaut syndrome pathology without localization with drop attacks.

OBJECTIVE: To describe endoscopic-assisted complete corpus callosotomy combined with anterior, hippocampal, and posterior commissurotomy.

METHODS: Patients with drug refractory epilepsy having drop attacks as the predominant seizure type, bilateral abnormalities on imaging, and moderate to severe mental retardation were included. All underwent a complete workup (including magnetic resonance imaging).

RESULTS: Patients (n = 16, mean age 11.4 ± 6.4 years, range 6-19 years) had a mean seizure frequency of 24.5 ± 19.8 days (range 1-60) and a mean intelligence quotient of 25.23 ± 10.71. All had syndromic diagnosis of Lennox-Gastaut syndrome, with the following etiologies: hypoxic insult (10), lissencephaly (2), bilateral band heterotropia (2), and microgyria and pachygria (2). Surgery included complete callosotomy and the section of anterior and posterior commissurotomy by microscopic approach through a mini craniotomy (11) and endoscopic-assisted approach (5). Complications included meningitis (1), hyperammonemic encephalopathy (2), and acute transient disconnection (5). There was no mortality or long-term morbidity. Mean follow-up was 18 ± 4.7 months (range 16-27 months). Drop attacks stopped in all. Seizure frequency/duration decreased >90% in 10 patients and >50% in 5 patients, and increased in 1 patient. All patients attained presurgical functional levels in 3 to 6 months. Child behavior checklist scores showed no deterioration. Parental questionnaires reported 90% satisfaction attributed to the control of drop attacks. The series was compared retrospectively with an age/sex-matched cohort (where a callosotomy only was performed), and showed better outcome for drop attacks (P < .003).

CONCLUSION: This preliminary study demonstrated the efficacy and safety of complete callosotomy with anterior, hippocampal, and posterior commissurotomy in Lennox-Gastaut syndrome (drop attacks) with moderate to severe mental retardation.

KEY WORDS: Anterior commissure, Commissurotomy, Corpus callosotomy, Drop attacks, Epilepsy surgery, Lennox-Gastaut syndrome, Pediatric, Posterior commissure

ABBREVIATIONS: AC, anterior commissure; ACT, anterior commissurotomy; CBCL, child behavior check list; CC, corpus callosotomy; HC, hippocampal; HCT, hippocampal commissurotomy; IQ, intelligence quotient; PC, posterior commissure; PCT, posterior commissurotomy

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A complete CC, while being more effective, is still considered as a palliative procedure. Studies that have compared anterior CC, staged CC, and single-stage CC have found that single-stage CC does not have higher complications.

Commissural sectioning (ACT, anterior commissurotomy; HCT, hippocampal commissurotomy; and PCT, posterior commissurotomy) was tried in the late seventies with success but was abandoned because of morbidities (mostly related to disconnection) in a few cases. In animal models, division of corpus callosum has been useful in the management of secondarily generalized epilepsies, but there is a lack of homogeneity in experimental studies to see the effect of anterior hippocampal and posterior commissurotomy on the generalization of discharges.

The current study includes patients who had severe LGS with disabling drop attacks. All had moderate to severe mental retardation. Hence, we assumed that a CC with anterior, hippocampal, and posterior commissurotomy might not result in a significant morbidity, while providing them the best possible option for seizure freedom by providing a complete “interhemispheric disconnection.”

Currently, CC is being increasingly replaced with vagal nerve stimulation, mostly because the former is considered as a palliative “destructive” surgery. More recent studies have demonstrated that after CC, in some patients, there is a better localization of the epileptogenic focus. A “better” interhemispheric disconnection may thus provide a better outcome of surgery. To the best of our knowledge, we have not come across an article that has combined a complete CC with ACT, HCT, and PCT. In addition, this is the first article in the literature to describe an endoscopic-assisted approach.

METHODS

This is a prospective, observational study. The study was approved by the institute’s ethics committee, performed according to the guidelines of Medical Research Council. The data in this prospective study were collected from October 2012 to December 2013. All patients underwent a presurgical evaluation that included video electroencephalography and magnetic resonance imaging (3T epilepsy protocol MRI), as already described in earlier studies. Single-photon emission computed tomography interictal and ictal and positron emission tomography were performed where necessary. Magnetoencephalography was performed in the last 5 cases.

Inclusion criteria included patients with LGS with multiple drop attacks as the predominant seizure type along with no single lateralization/localization of epileptiform zone/network; drop attacks as the predominant seizure type along with no single lateralization/localization of epileptiform zone/network; and absence of focal, predominantly left-sided, epilepsy. All had moderate to severe mental retardation. Hence, we assumed that a CC with anterior, hippocampal, and posterior commissurotomy might not result in a significant morbidity, while providing them the best possible option for seizure freedom by providing a complete “interhemispheric disconnection.”

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Neuropsychological and Behavioral Evaluation

All patients were assessed for social quotient using the Vineland Social Maturity Scale. For seizure outcome characterization and parental satisfaction, the scale adopted by Iwasaki et al was used. Child behavior check list (CBCL) score (ASEBA, Inc.) was adopted for behavioral assessments (113 items for parents). CBCL scores >60 indicated borderline or at-risk children, whereas scores >64 indicated significant clinical behavioral problems.

Surgical Technique

The patient was placed supine, neutral with head fixed in a head clamp. A small 5- to 6-cm transverse skin incision was placed a centimeter in front of the coronal suture, the craniotomy was 4 × 3 cm longitudinal (Figure 1). The final site of the craniotomy was determined by using neuronavigation (to avoid veins). All surgeries were performed in an operating room with an intraoperative MRI. Following dural opening, interhemispheric fissure was accessed and cisternal cerebrospinal fluid was released to make the brain lax. The first 11 cases were performed under a microscope with additional help from an endoscope. The last 5 cases were performed with endoscopic assistance only through a mini craniotomy (see Video, Supplemental Digital Content, http://links.lww.com/NEU/A786).

Once the corpus callosum was sectioned completely, the septae on either side of the cistem were separated. First, the anterior commissure (AC) was divided. The hippocampal commissure was divided by separating the septae and following it posteriorly. The hippocampal commissure is located at the level of the posterior part of the body of CC or just in front of the splenium. To the best of our knowledge, we have not come across an article that has combined a complete CC with ACT, HCT, and PCT. In addition, this is the first article in the literature to describe an endoscopic-assisted approach.

Outcome Assessment

All patients were assessed at 3, 6, 9, and 12 months initially and then every 6 months. Routine EEGs were performed at 3 months and later on as per the clinical decision of the neurologist 1 year later. Detailed neuropsychological assessments were conducted at 1 year. Seizure outcomes were recorded at last outpatient follow-up. Postoperative MRI was performed once immediately at the time of surgery and then scheduled on follow-up between 3 to 7 months (Figure 2).

RESULTS

Demographics

Sixteen patients (mean age: 10 ± 5.9 [range 2-25], 11 males) were recruited. Seizure onset was <1 month after birth in 8 patients, and, in all others, seizure onset ranged from birth to 5 years (mean 22.48 ± 31.77 months). Mean duration of epilepsy was 10 ± 6.4 years. The mean seizure frequency was 24.5 ± 19.8/day (range 1-60). Drop attacks were present in all along with tonic seizures (11), tonic-clonic (10), absence (2), myoclonic seizures (2), and focal dyscognitive seizures (2). Syndromic diagnosis of LGS (with multiple seizure semiologies) was made in all patients. Etiological cause included previous hypoxic insult in 10 patients (forceps delivery, meconium aspiration, hypoglycemia, and low birth weight with birth presentation), and lissencephaly, bilateral band heterotropia,
FIGURE 1. Figure shows the stepwise execution of the procedure from skin incision (A), craniotomy (B), and bone flap size (C) followed by sectioning of corpus callosum (D). After completing the complete section of corpus callosum, anterior (E) and posterior (G) commissures were identified (arrows) and sectioned respectively (F, H). Postoperative magnetic resonance imaging shows sectioned corpus callosum (I) and posterior commissure.
and microgyria/pachygyria in 2 patients each (Table 1). Change in the type of seizures was encountered in 9 patients. On admission, profound mental retardation with intelligence quotients (IQ) <20 was encountered in 7, severe mental retardation (IQ 20-34) was encountered in 7, and moderate mental retardation (IQ 35-49) was encountered in 2 patients (Tables 1 and 2).

Surgical Details

Eleven patients underwent complete CC, ACT, HCT, and PCT through a mini craniotomy (4 × 3 cm) with both microscopic and endoscopic assistance. Five patients underwent surgery with endoscopic assistance only through a mini craniotomy. No intraoperative complications were noted. The average stay in the intensive care unit was 2 days, median 2, with a range of 1 to 5 days. The mean blood loss was 85 ± 24.5 mL. The mean duration of microscope surgery was 153 (+27) minutes vs 124 (+29) minutes for endoscopic-assisted surgery (average for all surgeries: 144 minutes ± 30 minutes). The duration of the first 3 endoscopic surgeries was comparable to the microscopic surgeries. Most of the time was lost in setting up endoscopic equipment rather than the actual surgery. The duration of the last 2 endoscopic surgeries reduced significantly (Table 1). It should be also mentioned that, in all microscopic surgeries, the endoscope was used along with the microscope. In Table 1 it is interesting to note that the duration of case 16 is almost half of that of case 1.

Seizure Outcomes

Mean follow-up was 18 ± 4.7 months (range 15-26 months). There was a complete improvement in drop attacks in all patients. Significant decrease (>90%) in seizure frequency was noted in 10 patients, moderate reduction (>50%) in 5 patients, whereas increased seizure frequency was seen in 1 patient (Table 2). Decrease in frequency was observed in all types of seizures in these patients (tonic, tonic-clonic, absence, and myoclonic seizures). One patient initially underwent a complete callosotomy (25-year-old woman, case 7, Table 1) only. Following this, the patient went into status on the third postoperative day. Bedside electroencephalogram showed continuous nonconvulsive status epilepticus with ictal discharges from bilateral centroparietal areas. She was taken up for surgery in emergency; an additional ACT, HCT, and PCT were performed. After this, the seizures stopped. One patient encountered increased duration of seizure with a change of seizure type from spasms to unilateral tonic seizures of long duration.

Neuropsychological Outcomes

Aggression in behavior of patients was noted in 8 (first 3 months); this was reduced in 6 to 9 months in 3 patients. The mean IQ preoperatively was 25.23 ± 10.71, which did not deteriorate following surgery (mean score after surgery: 26.43 ± 11.41 at 6 months and 26.87 ± 11.95 at 1 year). Behavioral parameters, in particular, social contacts, attention span, and learning, also did not show deterioration. Detailed social
quotients analysis (at 6 and 12 months) did not show any deterioration. CBCL scores are summarized in Table 2 and also revealed no significant deterioration (rather improved mildly after surgery). The mean preoperative CBCL was 69.25 ± 2.5 in comparison with the postoperative score of 61.81 ± 3.8 (Table 2) at 1-year follow-up. On the parental questionnaire, 11 parents were satisfied with the surgical results and agreed to recommend this surgery to others.

**Control Cohort**

The study group was compared with a similar cohort (n = 16, mean age 12 ± 4.7 years, range of 4-21 years) (Table 3), where a complete CC only was performed. The mean age of onset of seizures was 26.7 ± 29.1 months, and mean seizure frequency was 10.3 ± 4.8/day (much less than the study group). All had drop attacks with multiple other seizure types. Four patients had profoundly low IQ (< 20), 3 had severely low IQ (20-34), 4 had moderately low IQ (35-49), and the remaining 5 had an IQ > 49. Following a CC, drop attacks were relieved (>90%) in 10 of 16 (62%), and other seizure types were relieved >90% in 7 of 16 (43%) at a mean follow-up of 16.4 months (13.2-21 months). On applying the Fisher exact test there was a significant difference in study and control groups for drop attacks (P = .003), being better in the case group. However, there was no significant difference for other seizure types (P = .240).

### Complications

Four patients had evidence of acute disconnection, characterized by confusion and limb apraxia of the nondominant side, and buccal apraxia (with pooling of saliva). This improved during the hospital stay to their preoperative functional levels. Two patients developed hyperammonemic encephalopathy, which required the discontinuation of valproate and the administration of lactulose. One patient developed bacterial meningitis and was treated appropriately. Mean hospital stay was 9.5 ± 5.1 days (5-20 days). No mortality or long-term procedural morbidity was recorded. Although it was not possible to examine the detailed extraocular movements because of the severe deranged cognitive status of the patients, none of the patients had contralateral light reflex. This did not affect them or their caregiving in any manner.

### Discussion

Complete callosal sectioning (first introduced by Van Wagenen in 1940) is a very effective “palliative” procedure for breaking secondary bilateral synchrony and alleviating drop attacks, with more than 90% improvement in drops with reasonable long-term remission. Various authors have tried different combinations: Watson (1968): complete CC + HCT; Wilson (1978); complete CC; Gloor (1980); complete CC + ACT; and Gates (1984): complete CC + HCT. Most of
these authors reported 10% to 20% of primary nonresponders and close to 30% of patients experienced further relapses in the next few years with outcomes mostly remaining stable thereafter.12,13 The common reasons cited for callosal sections failing to alleviate drop attacks or their recurrence is the possibility of transmission of epileptiform activity through other interhemispheric pathways like anterior, posterior, and hippocampal commissures.13,38-40 Using diffusion tensor imaging, Jang and Kwon (2013, 2014) have demonstrated a much wider connection of the fornix to include the cerebral cortex (precentral gyrus, postcentral gyrus, and posterior parietal cortex) and also the brainstem through the thalamus.41-43 The AC connects temporal lobes,39 whereas the hippocampal commissure (PC), mostly considered as rudimentary in humans, connects both the hippocampi and joins both the bodies of the fornices just under the posterior part of the body of the corpus callosum.38,44 Thus, division of anterior and hippocampal commissures may be expected to have a significant effect to reduce the seizure burden.

The main complication of the earlier series combining a complete CC with either ACT or HCT commissurotomies was the morbidity associated with acute disconnection.35-37,46-48 Similar complications and seizure outcome profiles were also reported in contemporary series.19,35,49 Although we observed acute disconnection syndromes, they did not alter the functional status of our patients. Even though all our patients had moderate to severe mental retardation with severe epilepsy, there was no deterioration (rather mild improvement) after surgery. One of the reasons could be because the patients were already severely compromised in their cognitive status, so that an additional disconnection may not alter their quality of life or leave a permanent disability. On the contrary, relief of disabling seizures was perceived as the biggest factor of improvement by parents in the postoperative period.

Recently, surgeries using smaller craniotomies have been performed more frequently for epilepsy surgeries like peri-insular hemispherotomies and even for anterior corpus callosotomies.6,44 More recently, an endoscopic-assisted hemispherotomy through a transcortical route has been described.45 In the present series, we performed a complete callosal sectioning along with section of AC, hippocampal (HC), and PC using a small craniotomy in the first 11 cases. This was followed by the use of an endoscopic-assisted approach only in the last 5 cases. Our study is the first of its kind to demonstrate the utility and safety of this approach for CC, AC, HC, and PC division. We also believe that an endoscopic-assisted approach through a mini craniotomy

| Table 2. Seizure Outcomes and Neuropsychological Assessments in the Cases (n = 16) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Seizure Outcomes** | **Drop Attacks After Surgery (Present or Absent)** | **Intelligence/Social Quotient** | **CBSL Scores (Child Behavior Check List)** |
| **Patient No.** | **% Decrease in Seizure Frequency** | **Presurgery** | **Postsurgery (6 mo)** | **Postsurgery (12 mo)** | **Presurgery** | **Postsurgery (12 mo)** |
| 1 | >50 | Absent | 44.81 | Moderate | 48.1 | 49.9 | 69 | 59 |
| 2 | >90 | Absent | 29.4 | Severe | 30.2 | 24.8 | 70 | 62 |
| 3 | >90 | Absent | 33.1 | Severe | 39.1 | 39.4 | 67 | 60 |
| 4 | >90 | Absent | 19.1 | Profound | 19.2 | 19.4 | 70 | 64 |
| 5 | >50 | Absent | 15.91 | Moderate | 19.53 | 23.4 | 68 | 65 |
| 6 | >90 | Absent | 38.51 | Profound | 39.45 | 49.6 | 72 | 65 |
| 7 | Status immediate post op followed by >90 improvement | Absent | 25.3 | Severe | 23.8 | 19.1 | 75 | 72 |
| 8 | >90 | Absent | 17.19 | Profound | 18.6 | 18.8 | 69 | 65 |
| 9 | >90 | Absent | 32.6 | Severe | 33.2 | 35.6 | 68 | 61 |
| 10 | >90 | Absent | 9.34 | Profound | 8.57 | 8.68 | 70 | 64 |
| 11 | >90 | Absent | 6.01 | Profound | 7.05 | 8.1 | 65 | 58 |
| 12 | >50 | Absent | 18.2 | Profound | 21 | 21 | 71 | 58 |
| 13 | >50 | Absent | 32 | Severe | 32.4 | 34 | 67 | 59 |
| 14 | >90 | Absent | 30 | Severe | 31.2 | 36 | 66 | 57 |
| 15 | Worse | Absent | 19.2 | Profound | 17.3 | 17 | 72 | 61 |
| 16 | >90 | Absent | 33 | Severe | 34.2 | 35.2 | 69 | 59 |
**TABLE 3. Table Showing the Outcome in the Control Cohort**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/ Sex</th>
<th>Seizure Onset (mo)</th>
<th>Seizure Types</th>
<th>Perinatal Insult</th>
<th>Imaging</th>
<th>Intelligence Level: Mild: IQ &gt; 49, Moderate: IQ 35-49, Severe: IQ 20-35, Profound: IQ &lt; 20</th>
<th>Outcome: Drop Attacks Relief &gt;90%, Present or Absent (Mean Follow up 16.4 mo)</th>
<th>Drop attacks After Surgery (Present or Absent)</th>
<th>Outcome: Other Seizures Relief &gt;90% Present or Absent (Mean Follow up 16.4 mo)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>17/F</td>
<td>42</td>
<td>D, T-C, A</td>
<td>Present</td>
<td>No substrate, brain shrunken because of epileptic encephalopathy</td>
<td>Moderate</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>2</td>
<td>16/M</td>
<td>6</td>
<td>D, T-C, A</td>
<td>Present</td>
<td>No substrate, brain shrunken because of epileptic encephalopathy</td>
<td>Mild</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>13/M</td>
<td>36</td>
<td>D, T, T-C, FDS</td>
<td>Present</td>
<td>HIE</td>
<td>Severe</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>14/M</td>
<td>3</td>
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<td>Present</td>
<td>No substrate, brain shrunken because of epileptic encephalopathy</td>
<td>Mild</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>5</td>
<td>16/F</td>
<td>4</td>
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<tr>
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<tr>
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<td>No substrate, brain shrunken because of epileptic encephalopathy</td>
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<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>8</td>
<td>7/F</td>
<td>4</td>
<td>T, SS, M</td>
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<td>HIE</td>
<td>Profound</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>9</td>
<td>12/M</td>
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<td>Severe</td>
<td>Present</td>
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<td>Present</td>
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<tr>
<td>10</td>
<td>16/M</td>
<td>68</td>
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<td>No substrate, brain shrunken because of epileptic encephalopathy</td>
<td>Moderate</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>11</td>
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<tr>
<td>14</td>
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<td>T, SS, M</td>
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<td>Absent</td>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>15</td>
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<td>HIE</td>
<td>Mild</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

*Explanation for the outcome: Column 9 shows the patients where a control of drop attacks >90% is present or absent. Column 10 shows patients with 100% control of drop attacks, Column 11 shows the relief of other types of seizures.*

**Intelligence level:**
- Profound: IQ < 20
- Severe: IQ 20-34
- Moderate: IQ 35-49
- Mild: IQ > 49

**Imaging:**
- No substrate
- Brain shrunken because of epileptic encephalopathy

**Seizure Types:**
- D: head drops
- T: tonic seizures
- T-C: tonic clonic
- A: absences
- M: myoclonic seizures
- ES: epileptic spasms
- FDS: focal dyscognitive seizures
- HIE: hypoxic ischemic encephalopathy
helps minimize unnecessary brain exposure and reduces blood loss. However, in 1 case, we had to extend the craniotomy because of the presence of large veins at the site of the craniotomy. It does become important to localize the venous anatomy preoperatively (MRI with gadolinium along with susceptibility-weighted imaging) to plan the optimal location for performing the craniotomy. Overall, we believe that, with some experience, the endoscopic-assisted approach through a “mini craniotomy” is feasible and is of advantage in performing this procedure (see Video, Supplemental Digital Content, http://links.lww.com/NEU/A786).

Neurological complications are reported in all major series in the magnitude of 2% to 5% with permanent sequelae in 5% of patients. We did not encounter any motor deficits or permanent deficits. However, postoperative akinetik state, buccal apraxia manifested as drooling of saliva, and limb apraxia were common. We believe that all these changes are due to acute disconnection syndromes, which were seen in 4 patients and persisted from weeks to months in a few patients. However, it improved in all patients within 3 to 6 months. In addition, improvement in seizure outcome and cognitive status compensated adequately this short-term morbidity.

However, despite the limitations mentioned below, the study did succeed in the objective of establishing the safety, efficacy, and acceptable morbidity of CC combined with anterior, hippocampal, and posterior commissurotomy. It also demonstrated a similar efficacy, if not better, compared with complete CC alone. Long-term follow-up of larger cohorts and comparison studies are needed for better understanding. Also, for the first time, the authors demonstrated a key hole endoscopic-assisted CC with anterior, hippocampal, and posterior commissurotomy.

Limitations

The biggest limitation of this study is the fact that it is not randomized and has been performed in a relatively small cohort. We have tried to compensate this to some extent by comparing this with a retrospective cohort. The follow-up is also relatively short. It also remains to be seen how safe the procedure would be in a patient who has a much better preserved cognitive status.

CONCLUSION

Complete corpus callosotomy combined with anterior, hippocampal, and posterior commissurotomy performed in patients with severe drop attacks and nonlocalizing epilepsy has been demonstrated to be safe and efficacious in LGS. Drop attacks ceased completely in all patients, and there was a significant improvement in all other seizure types (>90% reduction in 66% of cases). This was also accompanied with a significant improvement in cognition. We would also be hesitant at this stage to subject this procedure in patients with well-preserved cognitive status. Larger future studies, especially those involving blind ing this procedure with CC only, may be helpful in further establishing its role.

Disclosures

The study is part of Centre of Excellence for Epilepsy and is funded by department of science and Technology. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES
