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Prognostic value of electrocorticography findings during callosotomy in children with Lennox—Gastaut syndrome

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Summary

Objective: To analyze findings and acute changes in electrocorticograms (ECoGs) obtained during corpus callosotomy in order to identify any relationships with the postoperative outcome of seizure activity.
Methods: We retrospectively analyzed ECoGs obtained during anterior callosotomy (4—6 cm) in 48 patients with Lennox—Gastaut syndrome (32 boys and 16 girls, age 1—20 years, mean age 7.6 years) who underwent surgery between July 1993 and November 1996 to correlate recording findings with postoperative seizure activity. At the time of analysis, all patients had been followed postoperatively for more than 4 years.
Results: Of 48 patients, 31 (64.6%) had significant improvement in seizure control after surgery. In pre-excisional ECoGs, 38 (79.2%) of 48 patients had bisynchronous epileptiform discharges. Patients (23 of 33 patients, 69.7%) with significant blockage of bisynchronous discharges recorded during callosotomy achieved the best post-operative seizure outcomes, but the difference did not reach statistical significance ($P > 0.05$).
Conclusions: Based on our experience, changes in ECoG during callosotomy do not predict postoperative seizure outcome. Insignificant blockage of bisynchronous epileptiform discharges in ECoGs during callosotomy does not predict a worse prognosis than that associated with significant intraoperative blockage.
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Introduction

Since Van Wagenen and Herren reported the first case of corpus callosotomy in 1940, callosotomy has been widely applied in patients with Lennox—Gastaut syndrome (LGS) who experience frequent falls due to seizures based on the hypothesis that seizure activity spreads between the hemispheres mainly through the corpus callosum.[1]

Only a few reports of intraoperative electroencephalographic (EEG) findings and changes during corpus callosotomy have been published.[2,3] The first intraoperative EEG during callosotomy was done by Torres and French in 1937.[2] Fiol et al. used intraoperative surface EEG monitoring as a guide to extent of callosotomy and concluded it was not helpful.[3] Ragazzo et al. used mesial surface-electrocorticographic (ECoG) recording from both frontal and parietal lobes during partial callosotomy, and their findings correlated with pre- and postoperative EEG patterns in light of concepts of generalized epilepsies.[4]

Previous studies have identified several (often inconsistent) clinical factors predictive of a good or bad seizure outcome with callosotomy. They include IQ, lateralized brain lesions by neuroimaging, lateralized interictal scalp EEG abnormalities, changes in ictal scalp EEG patterns pre- and post-surgery, seizure type, and extent of callosal section.[5] Recently, Hanson et al. used ictal EEG as a predictive factor for outcome following corpus callosum section in adults and found that the ictal EEG but not other factors is able to identify a group of patients who have a better than 90% chance for total or nearly total resolution of seizures causing sudden falls.[6]

In designing the current study, we assumed that if there were marked blockage of bisynchronous epileptiform discharges (EDs) apparent in ECoG recordings during callosotomy, secondary generalized epilepsies resulting from interhemispheric spread of EDs would be prevented and postoperative prognosis would be good. Thus, the ECoG change can predict the callosotomy effect.

Methods

Selection of patients

The present series was drawn from all eligible subjects who received anterior corpus callosotomy at Taipei Veterans General Hospital, Taiwan, between July 1993 and November 1996. All patients fulfilled the following inclusion criteria: (1) Lennox—Gastaut syndrome; (2) medically intractable; (3) high-quality intraoperative ECoG recordings. Lennox—Gastaut syndrome is defined by an electroclinical triad of generalized slow spike-and-wave complexes in the EEG, multiple types of epileptic seizures, and slow mental development. Medical intractability

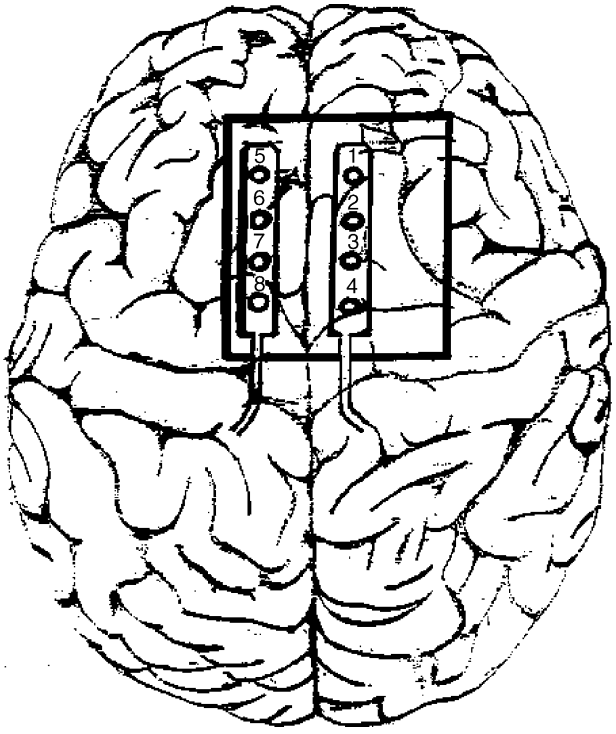

Figure 1 Positions of the two 4 × 1 electrode strips over bilateral frontal cortex during ECoG recording.

was defined as daily or weekly seizures with potential injury caused by cloudiness of consciousness or epileptic falls from atonic, myoclonic, or generalized seizures. Seizures were required to be refractory to most major commercially available anticonvulsants in Taiwan and occurring despite drug serum concentrations within documented therapeutic levels. In addition, seizures had to occur with a frequency of more than two episodes per month without 2 weeks free of seizures. Patients needed to have been supervised closely for at least 1 year under a qualified epileptologist.

Method for ECoG recording

A single C-shape incision along the coronary suture with cross midline right frontotemporal craniotomy was made. A 4×1 electrode strip was put in contact directly with the cortex of the right frontal convexity after removal of the dura. Another 4×1 electrode strip was inserted through a small incision hole on the dura into the subdural region in contact with the left frontal convexity. Both electrode strips were in the homologous corresponding position 1.5 cm away from the midline and running in parallel with each other (Fig. 1). Occasionally, 6×1 or 4×5 electrode strips were used instead of 4×1 strips because of technical problems. A pre-excision ECoG was performed for 30 min with an 18-channel Grass EEG machine. A post-excision ECoG was performed for another 30 min after the corpus callosum was divided from the genu backward to the tip of the hippocampal commissure for about 4—6 cm (anterior 2/3 to 4/5 corpus callosotomy).

Anesthesia during callosotomy

No patients were given any premedication prior to surgery. Anesthesia was induced with 2—2.5% inspired concentration halothane and nitrous oxide in oxygen (3:2) via a face mask under manually controlled ventilation. Atropine sulphate (0.015 mg/kg) and pancuronium bromide (1.9 mg/kg) were administered to facilitate endotracheal intubation after an intravenous (i.v.) line had been established. Anesthesia was maintained with a low concentration of isofluorane without nitrous oxide and continuous infusion of fentanyl (5—8 mg/kg/h, i.v.). Neuromuscular block was maintained with pancuronium bromide (0.1 mg/kg, i.v.) to provide adequate surgical conditions.

Grading of postoperative seizure outcome

Postoperative seizure outcome was classified into one of six grades: Grade 1, seizure free without anticonvulsant therapy; Grade 2, seizure free with anticonvulsant therapy; Grade 3, seizure reduction of more than 50%; Grade 4, seizure reduction less than 50%; Grade 5, no change in either frequency or severity of seizures; and Grade 6, worse seizures. Significant improvement was defined as having more than 50% reduction in postoperative seizure frequency, which included Grades 1—3.

Changes in ECoG

Changes in ECoG were categorized into three large groups according to degree of blockage of bisynchronous EDs intraoperatively: Group 1, significant blockage (>50%) of bisynchronous EDs (including EDs lateralized to one side, EDs becoming independent over both sides, and complete disappearance of EDs); Group 2, insignificant blockage (<50%) of bisynchronous EDs; Group 3, few EDs or EDs already independent over both sides before callosotomy (Figs. 2—4).

Statistical analysis

Chi-square test was used for comparison of localization of EDs and postoperative seizure outcome between groups. For all tests, a *P*-value of <0.05 was considered statistically significant.

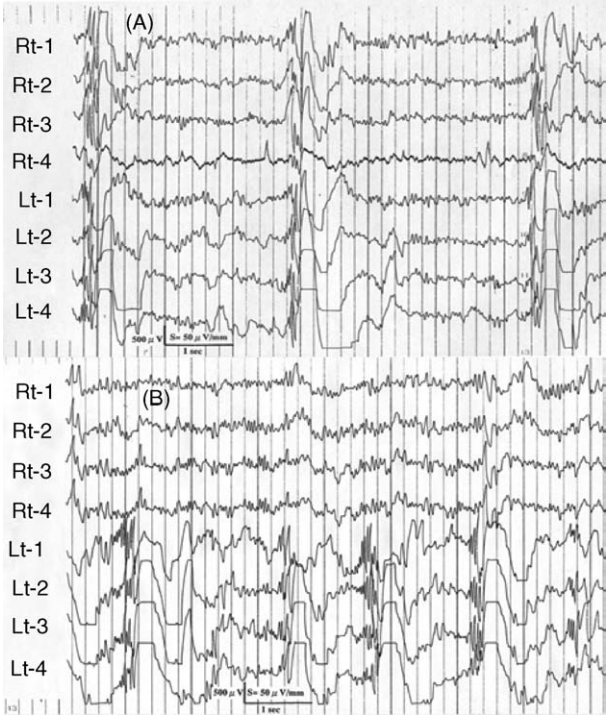

Figure 2 Example of ECoG change: Group 1. Bisynchronous EDs become lateralized to one side after callosotomy. (A) Before callosotomy: bisynchronous spike- or polyspike-and-wave complexes. (B) After callosotomy: EDs lateralized to left side.

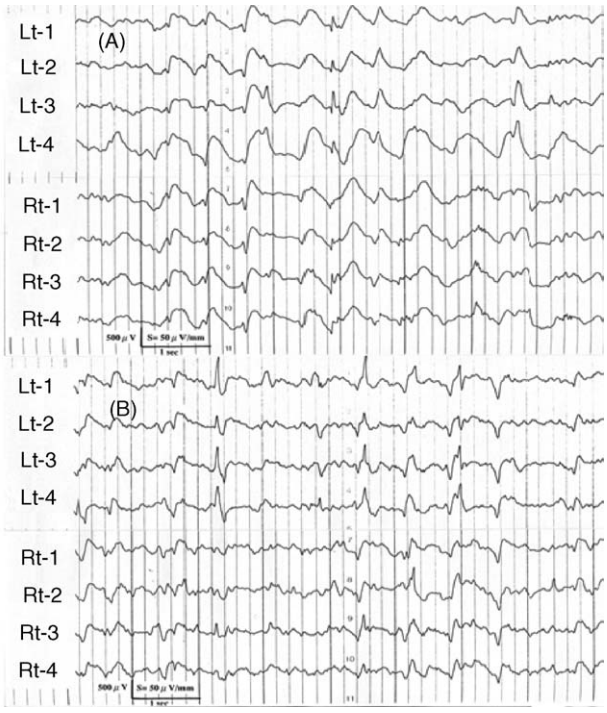

Figure 3 Example of ECoG change: Group 2. Bisynchronous EDs were only mildly blocked after callosotomy. (A) Before callosotomy: frequent bisynchronous polyspikes and spikes. (B) After callosotomy: most spikes still occurred bisynchronously.

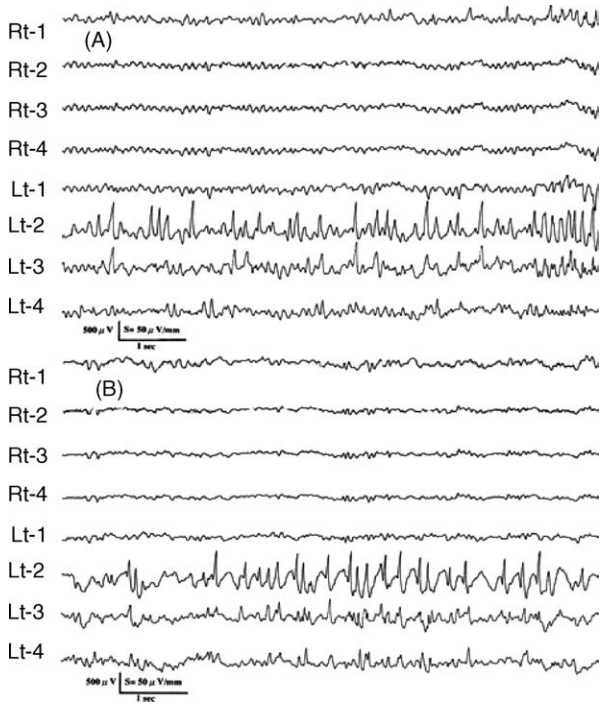

Figure 4 Example of ECoG change: Group 3. EDs were already independent before callosotomy. (A) Before callosotomy: active trains of spikes over left side. (B) After callosotomy: EDs without significant change.

Results

Of the 48 patients, there were 33 boys and 15 girls aged from 1 to 20 years (mean, 7.6 years). Onset of epilepsy ranged from less than 1 day to 10 years (mean, 2.0 years). Duration between onset of epilepsy and callosotomy ranged from 1 to 14 years (mean, 5.6 years). Total follow-up time was from 4 to 7.5 years (mean 5.8 years).

When postoperative seizure outcome was graded, no patient was Grade 1; 9 patients (18.8%) were Grade 2; 22 patients (45.8%) were Grade 3; 10 patients were Grade 4 (20.8%); 7 patients (14.6%) were Grade 5; and none was Grade 1 or 6. A total of 31 patients (64.6%) achieved significant improvement (Table 1).

According to the ECoG categorization, ECoG findings were stratified with 33 patients (68.8%) in Group 1, 5 patients (10.4%) in Group 2, and 10 patients (20.8%) in Group 3.

The number and percentage of patients with significant improvement in each group was as follows: Group 1, 23 of 33 patients (69.7%); Group 2, 3 of 5 patients (60%); Group 3, 5 of 10 patients (50%) (Table 1).

When we compared the overall number of patients with significant improvement in postoperative

Table 1 Relationship between electrocorticographic changes during callosotomy and postoperative seizure outcome.

Intraoperative ECoG change	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6	Significant improvement (Grades 2 + 3)	Insignificant improvement (Grades 4 + 5 + 6)
Group 1 (n = 33, 68.8%)	0	8	15	5	5	0	23 (69.7%)	10 (30.3%)
Group 2 (n = 5, 10.4%)	0	1	2	1	1	0	3 (60%)	2 (40%)
Groups 1 + 2 (n = 38, 79.2%)	0	9	17	6	6	0	26 (68.4%)	12 (31.6%)
Group 3 (n = 10, 20.8%)	0	0	5	4	1	0	5 (50%)	5 (50%)
Total (n = 48)	0 (0%)	9 (18.8%)	22 (45.8%)	10 (20.8%)	7 (14.6%)	0 (0%)	31 (64.6%)	71 (35.4%)

Group 1: significant blockage (>50%) of bisynchronous EDs (including EDs lateralized to one side, EDs becoming independent over both sides, and complete disappearance of EDs). Group 2: insignificant blockage (<50%) of bisynchronous EDs. Group 3: few EDs or EDs already independent over both sides before callosotomy.

seizure outcome between Groups 1 (marked blockage of bisynchronous EDs) and 2 (mild or no blockage of bisynchronous EDs), the result was 23 patients (69.7%) versus 3 patients (60.0%). The difference was not statistically significant (Table 1).

When we compared postoperative outcome between presence of bisynchronous EDs before callosotomy (Groups 1 and 2) and few EDs or EDs already independent over both sides before callosotomy (Group 3), significant improvement after callosotomy was seen in 68.4% (26 of 38 patients) versus 50% (5 of 10 patients). Again, the difference was not significant (Table 1).

Discussion

There are several interhemispheric commissures, including the corpus callosum, anterior commissure, posterior commissure, hippocampal commissure, and massa intermedia of the thalamus. The corpus callosum has been thought to be the most important, especially its anterior and middle portions. The importance of the anterior portion was fully supported by the high incidence of Group 1 patients (33 of 48, 68.8%) in our series. The Groups 2 and 3 suggested that EDs spread through other pathways rather than corpus callosum.

The persistence of bisynchronous EDs after callosotomy in Group 2 patients (5 of 48, 10.4%) suggests that seizure activity in these patients spread interhemispherically via either the posterior portion of the corpus callosum or through other interhemispheric commissures mentioned above, but not as frequently as seen with Group 1. Gates and Wilson noted that generalized EDs could still continue to occur after complete callosotomy.[7,8] Their findings suggest that extra-corpus callosum interhemispheric pathways truly exist. Among them, the intrathalamic pathway is thought to be the most important. Kusske and Rush found that callosotomy could accelerate such thalamic spread of EDs.[9] Collins et al. successfully induced bilateral seizures from a unilateral focus in rats primarily through increasing activation of intrathalamic pathways.[10] Schwartzkroin et al. concluded that the cortical—thalamic system was a more potent mechanism for spread of epileptogenic activity from a cortical epileptogenic focus than homotopic spread via callosal fibers.[11]

In addition to seizure activity spread interhemispherically via posterior corpus callosum or intrathalamic pathways, other mechanisms might account for failure to control seizures after callosotomy. The midbrain reticular formation and substantia nigra are important for the occurrence of diffuse generalized discharges and generalized seizures.[12,13] Collins et al. successfully demonstrated in cat brains that, while seizure activity propagates horizontally across the callosum, it also descends vertically from the cortex to the anterior horn cells of the spinal cord.[9] During descent, the electrical signal branches into the centrecephalon, which may modify the intensity and quality of the discharges. It is possible that seizure activity spreading downward to the centrecephalon, probably through the reticular formation and substantia nigra through a corticoreticular-like pathway, diffusely projects backward to bilateral cerebral cortexes. This might also explain the high incidence of bisynchronous EDs still present after callosotomy in 5 of 48 patients (10.4%) in our series.

In our series, there was no statistically significant difference in the number of patients with significant improvement of postoperative seizure outcome between Groups 1 and 2 patients (69.7% versus 60.0%). This suggests that there is no significant relationship between blockage of bisynchronous EDs in ECoG after callosotomy and prognostic prediction, which is consistent with a previous study.[3] However, the sample size of Group 2 patients might have interfered with the analysis, and this point needs more exploration. Secondly, in our series there was no statistically significant difference in the number of patients with significant improvement of postoperative seizure outcome among Groups 1—3 (68.4% for 1 and 2 versus 50% for 3). This suggests that the presence of bisynchronous EDs before callosotomy does not predict postoperative outcome. Third, because main interhemispheric spreading is through the corpus callosum, the ECoG may be useful to predict prognosis for most patients of Lennox—Gautaut syndrome, as occurred in our Group 1 (significant improvement versus insignificant improvement = 69.7% versus 30.3%). However, this was not found in Group 2.

Recently, in an intraoperative observation of electrocorticogram and callosal compound action potentials, Ono et al. proposed that the interhemispheric recruitment of the epileptogenic state as a different role of the corpus callosum on epileptogenesis.[14] Matsuo et al. reported that corpus callosotomy unevenly reduced preoperative epileptiform discharges in both hemispheres, suggesting a facilitatory role played by the callosal neurons that enables the asymmetrical epileptogenic susceptible state of the two hemispheres to develop bisynchronous and bisymmetrical epileptiform discharges and conclude that corpus callosotomy decreased the quantity of the epileptiform discharges, suggesting the transhemispheric facilitation of seizure mechanisms. The role of corpus callosum may be

much more complicated than interhemispheric transfer of epileptiform discharges.[15]

Changes in the dosage or number of antiepilepsy drugs (AEDs) might influence the post-callostomy seizure outcome in few patients. Previous reports suggested retraction of the non-dominent hemisphere during callosotomy, that changes in pre- versus post-callosotomy ECoG patterns could be due to retraction of the right frontal lobe.[16] However, three main conclusions may be drawn from our findings. First, most of the bisynchronous EDs spread interhemispherically through the anterior portion of corpus callosum in our series of patients. Introperative ECoGs may be useful to predict prognosis for these patients. Second, greater blockage of bisynchronous EDs per ECoG does not predict better prognosis. Third, the presence of bisynchronous EDs in ECoG performed before callosotomy does not predict postoperative seizure outcome.

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