Callosal role in generation of epileptiform discharges: quantitative analysis of EEGs recorded in patients undergoing corpus callosotomy

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Abstract
Objective: Corpus callosotomy tends to decrease seizure frequency and severity rather than transforming the seizure pattern from a generalized form into a lateralized or a partial one. The finding implies that bisection of the corpus callosum (CC) disrupts the epileptogenicity itself. In order to gain further insight into the possible role played by the CC in intractable generalized epilepsy, quantitative analyses of long-term EEGs were performed.

Methods: Analyses were made of epileptiform discharges contained in the pre- and postoperative long-term EEGs in seven patients who had an anterior callosotomy for intractable epilepsy. The duration, number, and amplitude of all epileptiform burst activities were measured and statistically analyzed.

Results: After callosotomy, the total number of epileptiform burst activities, mean duration, and the total number of spike discharges decreased significantly. The two hemispheres could be divided into dominant and non-dominant ones as to the quantity of the residual epileptiform discharges.

Conclusions: 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.

Significance: Corpus callosotomy decreased the quantity of the epileptiform discharges, suggesting the transhemispheric facilitation of seizure mechanisms.

Introduction
In epilepsy, the putative role of the corpus callosum (CC) appears to be the pathophysiological transmission of epileptiform discharges from one hemisphere to another. In 1940, Van Wagenen and Herren reported results of commissurotomy including the CC “in an effort to limit the spread of a convulsive wave to one-half of the cerebrum” in 10 patients with epilepsy. The CC has been thought to be a major pathway for spread of epileptiform discharges from one hemisphere to the other for bilateral generalization (Van Wagenen and Herren, 1940; Bogen and Vogel, 1962). Several qualitative studies based on visual inspection have partly supported this view, that is, callosotomy significantly reduced bilaterally synchronous generalized epileptiform discharges, while total epileptiform discharges did not change (Gates et al., 1984; Spencer et al., 1985; Oguni et al., 1994).

Callosotomy does not necessarily abolish bilaterally synchronous interictal epileptiform discharges completely, even after complete section of the corpus callosum. This is true for generalized seizures, i.e., callosotomy frequently causes a reduction of seizure frequency and severity rather than causing the transformation of a generalized seizure to a lateralized or a partial
one. Thus, the incomplete diminution of bilaterally synchronous interictal epileptiform discharges may be interpreted to imply that epileptic discharges follow pathways, both across the CC and brainstem structures (Spencer et al., 1985, 1993). However, in some cases, seizures have been completely suppressed with normalization of EEG (Wada, 1979; Spencer et al., 1985; Gates et al., 1987; Baba et al. 1996).

These clinical observations are difficult to reconcile if the presumed role of the CC is exclusively transhemispheric transmission of epileptiform discharge. Rather, the findings seem to suggest that the CC is involved in the epileptogenic susceptibility state of the cerebral cortex, in the same manner as Bremer’s prescience as quoted by Bogen (1985): “Commissural synergy is capable of influencing the appearance and course of an epileptic seizure in a fashion other than that of transmission of above-threshold discharges. The probability of a tonic, reciprocal facilitation of homologous cortical areas suggests the possibility of a lowering of the threshold as the result of this constant interhemispheric dynamogenesis.”

If that is the case and the interictal epileptiform discharge is indicative of epileptogenicity, not only would the number of epileptiform discharges decrease but also the duration of consecutive bursting would be curtailed after callosotomy in accordance with decreased epileptogenic susceptibility. In order to test our hypothesis, we quantified all epileptiform discharges in long-term EEGs and performed statistical analyses of frequency, duration, and laterality of epileptiform discharges that were present before and after callosotomy.

Methods

Selection of patients

Seven patients (five males and two females) were randomly selected from patients who had undergone an anterior callosotomy (Purves et al., 1988) for intractable epilepsy at the National Nagasaki Medical Center (Baba et al., 1996). Long-term digital EEG recordings were performed in all patients two months prior to and one month after the operation. The ages of patients at the time of operation ranged from 10 to 53 years (mean: 26.8 years), and the number of years since first onset of seizures ranged from 5 to 40 years (mean: 19 years). Three of the patients had a known etiology: asphyxia in two patients and neonatal intracranial hemorrhage in one. The etiology was unknown in the remaining four patients.

Five patients had symptomatic generalized epilepsy (SGE) and two patients had frontal lobe epilepsy with no focal or lateralizing features. Types of seizures were tonic seizure (four patients), atypical absence (three patients), drop attacks (three patients), atonic seizure (one patient), and complex partial seizure (three patients). Of the patients with SGE, two had been diagnosed as Lennox-Gastaut syndrome. Despite these diverse clinical seizure types, their interictal EEG abnormality was characterized by anterior dominant bursts of bilaterally synchronous (slow) spike-and-wave activity.

EEG recordings and quantitative analysis

Long-term, monopolar, 16-channel digital scalp EEGs were recorded according to the 10-20 International System referenced to linked ears before and after the surgery in all subjects. Based on our routine procedure, EEG-video monitoring was carried out for 18 hours from 6 PM to 12AM of the next day. The subjects were allowed to disconnect their electrode leads temporarily as occasion demanded.
Under a visually guided graphical environment using a homemade computer system, the duration and amplitude of all visually identified epileptiform bursts were measured interactively. Burst activity is defined as more than one spike-and-wave. For example, if respective burst activities included five, three, and one spike-and-waves, they were counted as three burst activities and nine spike discharges. Amplitude was measured at the highest spike discharge within the burst activity.

Under a visually guided graphical environment using a homemade computer system, the whole EEG was reviewed and artefact-containing portions were discarded. The duration and amplitude of all visually identified epileptiform bursts (1710 preoperative and 1166 postoperative bursts in total) were measured interactively and independently at bilateral frontal and central electrode sites (F3/4 and C3/4), chosen because of commonly observed anterior dominant spike-and-wave features. All measurements were performed by only one person (A.M.). Eventual duration of analysis was from 7.7 to 18 hours (mean: 11.4 hours), and there was no significant difference between those of pre- and postcallosotomy (mean: 11.9 vs 10.9 hours, Wilcoxon’s signed rank test). Although the EEG necessarily included both waking and sleeping record, the ratio of awake and sleep periods was 1:2.9-3.4 in all analyzed records and not significantly different for both pre- and postcallosotomy in every patient (Wilcoxon’s signed rank test).

Duration, amplitude, and number of all epileptiform burst activities were independently measured at each electrode site (Fig. 1). We defined “burst activity” as having one or more spike-and-wave discharges at one electrode. Therefore, even a single spike-and-wave was treated as a (short) burst activity. Amplitude was measured at the highest peak of the spike within the burst activity. The total amount of spike discharge was defined as an hourly averaged count of epileptiform discharges among every electrode sites under consideration, and counted from each spike-and-wave burst. For example, respective burst activities that contained five, three, and one spike-and-wave discharges were counted as having three bursts with a total of nine spike discharges.

To study the overall profile of postoperative change in burst duration, each duration of burst activity was normalized (by subtracting the mean and then dividing by the standard deviation) within the corresponding individual to eliminate interindividual variations, then accumulated separately as pre- and postoperative histograms with a bin width of 0.5 S.D. Chi-square test was used to test the equality of pre- and postoperative distribution of the burst duration.

**Fig. 1. Measurement of EEG**

Under a visually guided graphical environment using a homemade computer system, the duration and amplitude of all visually identified epileptiform bursts were measured interactively. Burst activity is defined as more than one spike-and-wave. For example, if respective burst activities included five, three, and one spike-and-waves, they were counted as three burst activities and nine spike discharges. Amplitude was measured at the highest spike discharge within the burst activity.
A synchrony index was defined as a proportion of bursting events that occurred bilaterally at almost same moment regardless of a small time difference or amplitude difference. In addition, a laterality index was defined as the absolute value of \((R-L)/(R+L)\), where \(R\) and \(L\) are averaged values of the subjected measure (i.e., number of spike discharges, number of burst activities, or mean amplitude of spike discharges) in the right and left hemispheres, respectively. We used it to quantitatively evaluate the degree of symmetry/asymmetry between the two hemispheres, i.e., a larger laterality index indicates greater hemispheric difference.

Wilcoxon’s signed rank test was used for testing the difference between a pair of related measurements such as before and after surgery. In general, \(p<0.05\) was considered significant.

**Results**

Preoperatively, all patients had generalized, bilaterally synchronous, slow spike-and-wave discharges and all the bursts of epileptiform discharges were always bilaterally synchronous (i.e., synchrony index=1.00). Such bilateral synchrony was disrupted after surgery in all patients \((p<0.05, \text{Wilcoxon’s signed rank test})\), i.e., the mean postoperative synchrony index among all subjects was 0.31 (range: 0.02-0.83) compared to the preoperative value of 1.00.

Although considerable interindividual variations in each measure of epileptiform burst activity were present preoperatively, various degrees of reduction of both the total and mean duration of burst activity were noted postoperatively in all patients without exception \((p<0.05, \text{Wilcoxon’s signed rank test})\) (Fig. 2).

At the same time, the hourly number of bursts did not change significantly after callosotomy (decreased in five and increased in two patients), although, on the average, the number of bursts decreased slightly from 19.7/hr of preoperative frequency to 14.4/hr. To obtain further detail of postoperative change, the duration of preoperative 1710 and postoperative 1166 burst activities were

![Figure 2](image)

*Fig. 2. Changes of burst activity after callosotomy.*

Epileptic discharges decreased after callosotomy across all subjects in terms of both the total (left) and the mean (right) duration. Thus, the decrement was statistically significant \((p<0.05, \text{Wilcoxon’s signed rank test})\).
analyzed by means of comparing those distributions. Each measured duration was normalized within the corresponding individual to eliminate the interindividual variations, then pooled and separately accumulated with a bin width of 0.5 S.D. as pre- and postoperative histograms (Fig. 3). Postoperative frequency distribution of the burst durations (broken line) shifted significantly to the left as against the preoperative one (solid line) (p<0.01, Chi-square test). This finding indicates that the preoperatively present longer burst activities had significantly diminished while short burst activities, including single spike discharges, had increased postoperatively. Along with that, the total amount of spike discharges also significantly diminished, mainly due to shortening the burst duration in all patients to a different degree with a mean reduction rate of 0.59, with a range from 0.26 to 0.99 (p<0.05, Wilcoxon’s signed rank test) (Fig. 4). Such postoperative decrements of spike discharges were asymmetrical in all subjects and confirmed independently in every electrode sites.

The laterality indices as to the number of both spike (Fig. 5A) and burst discharge (Fig. 5B), and mean amplitude of spike discharge (Fig. 5C) increased in all patients, indicating a postoperative emergence of hemispheric asymmetry in the above measurements. There was virtually identical epileptiform activity in both hemispheres prior to surgery, and callosotomy affected unevenly depending on the hemisphere. This finding indicates the differential effect of callosotomy upon epileptiform discharge of the two hemispheres. Accordingly, the two hemispheres can be divided into dominant and non-dominant sides with respect to the presumed epileptogenicity on the basis of amount of residual epileptiform discharges. More epileptiform discharges remained in the former than in the latter after callosotomy. The mean rate of decrease in the spike discharge was 48% on the dominant side and 70% on the non-dominant side.

The outcome with respect to clinical seizures was a significant reduction (> 80%) in four
patients. The rest remained at a reduction of 50-80% in two patients, and a poor reduction of less than 50% in one patient. Although a seizure reduction to a greater or lesser extent was a common finding, no definite linear correlation was found between the residual amount of epileptiform discharges and clinical seizure outcomes.

Discussion

The CC is a bundle of axons originating from clustered neurons (CC neurons) widely distributed throughout the cerebral hemispheres (Kaas, 1995). Although the CC is a prominent structure in the brain, the number of callosally projecting neurons is no more than a few percent of the total number of cortical neurons, i.e., 15 billion (Lamantia and Rakic, 1990; Aboitiz et al., 1992). Thus, the direct contribution of the callosally projecting neurons to cortical epileptiform discharge could not be great. However, since the callosal neuron projects not only contralaterally through the CC but also ipsilaterally through collateral projections, the CC neuron has a potential of modulating neuronal activities of a widespread area in both cerebral hemispheres. Namely, the CC neurons could influence on the widespread cortical activities despite minimal direct contribution to the cortical EEG due to relative rarity of the CC neurons. When we refer to the potential role of the CC on epileptogenesis, not only the CC as a bundle of axons but also CC projecting neurons as its source are naturally included because they function as a whole, i.e., as a callosal neuronal system. We could assume that 1) most of the CC projecting neurons have bifurcated axons, one crossing the CC and another projecting ipsilaterally as a kind of association fiber; 2) most of these neurons and ipsilaterally projecting axons survive after callosotomy (Orihara et al., 1997); 3) these neurons have a reciprocal innervation with target neurons in principle; and 4) transcallosal activation of the CC neurons results in enhancement of the thalamo-cortical responses (Ono et al., 2002a). This effect could be manifested through the ipsilaterally projecting axons to the thalamo-cortical column neurons. Thus, blockade of transcallosal volleys by callosotomy will reduce basal activities of the formerly CC projecting neurons, and thereby result in less facilitatory influences over the ipsilateral hemisphere through the surviving collaterals.

Fig. 4. Postoperative decrement of spike discharges.

Comparison between the pre- and postoperative number of spike discharges in each subject showed that the total number of spike discharges decreased postoperatively in all subjects to a different degree, with a mean reduction rate of 0.59 with a range from 0.26 to 0.99 (p<0.05, Wilcoxon’s signed rank test). The postoperative decrement of spike discharges was also confirmed independently in all electrode sites under observation. In addition, the reduction rate was asymmetrical in all subjects.
It is generally conceived that the goal of corpus callosotomy is to prevent propagation of seizure discharge from one hemisphere to the other side to prevent its bilateralization, i.e. secondary generalization (Van Wagenen and Herren, 1940). This notion may be partly supported by EEG changes after callosotomy, i.e., preoperatively observed bilateral synchronous discharges became lateralized or desynchronized postoperatively (Gates et al., 1984; Spencer et al., 1985; Oguni et al., 1994).

However, callosotomy does not necessarily abolish bilaterally synchronous interictal epileptiform discharges even after complete section of the corpus callosum. This situation may be just as valid for generalized seizures, i.e., callosotomy frequently causes a reduction of seizure frequency and severity rather than causing transformation of a generalized seizure to a lateralized or a partial one (Gates et al., 1987; Purves et al., 1988; Spencer et al., 1988; Baba et al., 1996; Sorenson et al., 1997). While Spencer et al. (1984) have presented evidence that occasionally new or more intense partial seizures occur after CC section, the residual partial seizures could actually be fragments of previous generalized seizures, and the relative rarity of the incidence might raise doubts as to specificity as a direct effect of callosotomy. We further need to reexamine whether CC section actually produces more intense focal seizures. More interestingly, seizures have been completely suppressed with normalization of EEG in some cases (Wada, 1979; Spencer et al., 1985; Gates et al., 1987; Baba et al. 1996).

Although it is commonly accepted that callosotomy results in marked disruption of preoperatively present bilaterally synchronous epileptiform discharges, other outcomes as to epileptiform discharges have not been fully documented. One qualitative study that referred to the interictal epileptiform discharges simply stated that there was no significant difference in total amount of epileptiform discharges pre- and postoperatively without detailed explanation (Oguni et al., 1994). Gates et al. (1984) also reported that following callosotomy the frequency of all

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**Fig. 5.** Effect of callosotomy on the laterality of seizure discharge.

Laterality index was defined as the absolute value of \( (R-L)/(R+L) \), where \( R \) and \( L \) are the average values of each measure corresponding to the right and left hemispheres respectively. With respect to the number of spike discharges (A), the number of burst activities (B), and the mean amplitude of spike discharges(C), the laterality indices for every patient were all increased after callosotomy (p<0.05, Wilcoxon’s signed rank test). There was virtually identical epileptiform activity in both hemispheres prior to surgery, and callosotomy affected unevenly, depending on the hemisphere.

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epileptiform discharges was not reduced, but previously generalized epileptiform bursts became typically lateralized to one hemisphere. However, even in this report that analyzed a short-term routine EEG, the total amount of epileptiform discharges decreased in four out of six cases, while only a slight increase was observed in the rest. Taking a temporal fluctuation of the epileptogenic state into consideration, their result might be inconclusive. Besides, an obscure definition of the “total amount of epileptiform discharges” may confuse the adequate interpretation of their results. In cases where preoperatively generalized (bilateral) epileptiform discharges become lateralized completely to one hemisphere and the residual discharges remain unchanged within the unsubdued hemisphere after callosotomy, how should the total amount of epileptiform discharges be convincingly expressed?

In the present study, quantitative and statistical analyses of long-term 8-18 hour EEGs that included both sleeping and waking periods were designed to minimize variation due to intraindividual temporal fluctuation of epileptiform discharges. Furthermore, measurements were independently made at four electrode sites to evaluate localizing or lateralizing features. We defined the total amount of spike discharges as an hourly averaged count of epileptiform discharges among all electrode sites. This measure may be reasonably taken to represent the profile of the entire brain under consideration. As a result, it is evidenced that callosotomy resulted in significant reduction of both the total amount of spike discharge and the duration of burst activity, in addition to the disruption of bilateral synchrony as previously reported. This probably represents a sustained effect since it was present one month postoperatively and may suggest reciprocal facilitation of epileptic susceptible state via the corpus callosum.

Furthermore, postoperative quantitative difference in the amount of residual epileptiform discharges found between two hemispheres could be differentiated as dominant as against the non-dominant hemisphere with respect to the presumed epileptogenicity on the basis of amount of residual epileptiform discharges. This finding leads us to postulate putative asymmetry of pre-existing cortical epileptogenic susceptibility state between two hemispheres.

These observations are difficult to understand if the putative role of the CC is exclusively that of spreading the epileptic discharge from one hemisphere to another. As suggested previously (Wada, 1997), we believe that the underlying mechanisms for the postoperative reduction/arrest of epileptiform discharges would closely relate to the dynamic nature of the callosal system. Very recently, Ono et al. (2002b) successfully demonstrated, using an intraoperative direct recording of the callosal compound action potentials; rather, the cortically observed epileptiform discharge does not propagate to the contralateral hemisphere through the CC in a manner of an evoked potential, but both hemispheres independently generate epileptiform discharges at almost same moment through a kind of interhemispheric recruitment to epileptogenic state.

In this scenario, the CC is assumed to have a mutually facilitatory effect that enhances the susceptible state of both hemispheres (Rovit and Swiecicki, 1965; Ono et al., 2002a), leading to bilateral symmetry and synchrony (or nearly so) of the epileptiform discharge (Murchus, 1985; Ono et al., 2002b). The latter could have augmented the tendency to generalized seizure emission. Therefore, overt asymmetry and asynchrony, lateralization and the complete disappearance of epileptiform discharge following callosotomy may be understood if one assumes 1) the preoperative epileptogenic susceptible state to have been bilaterally potent but asymmetrical, potent but largely lateralized, and bilateral but only moderate, respectively, and 2) the facilitatory role played by the CC to enable mutual interaction and modulation of epileptogenic susceptible state of the two hemispheres in generalized epilepsy patients.

In the present study, most of our observations were limited to interictal phenomena, and we
have not directly measured epileptic seizure itself. Besides, it is an indisputable fact that the interictal amount of epileptiform discharges does not exclusively regulate clinical seizures. However, given that the probability of transition to ictal state correlates to a certain degree with the interictal state, interictal epileptiform discharges would be indicative of epileptogenicity in general. This assumption is supported, in part, by concurrent reduction/arrest of both interictal epileptiform discharges and clinical seizures following callosotomy, although its validity awaits future clarification of the exact mechanism of seizure initiation. Of course, preoperative prediction of the seizure outcome after callosotomy is clinically critical, and we further need a more relevant measure for potentiality of the ictal transition.

We conclude that the result of callosotomy on generalized epileptiform discharge in intractable generalized epilepsy can be explained by postulating that the CC has a facilitatory role that enables mutually enhancing interaction and modulation of an epileptogenic susceptible state between the two hemispheres.

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