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Centro-median stimulation yields additional seizure frequency and attention improvement in patients previously submitted to callosotomy

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ABSTRACT

Rationale: Deep brain stimulation (DBS) has been increasingly used in the treatment of refractory epilepsy over the last decade. We report on the outcome after thalamic centro-median (CM) DBS in patients with generalized epilepsy who had been previously treated with extended callosal section.
Methods: Four consecutive patients with generalized epilepsy who were previously submitted to callosal section and had at least 1 year of follow-up after deep brain implantation were studied. Age ranged from 19 to 44 years. All patients were submitted to bilateral CM thalamic DBS. Post-operative CT scans documented the electrode position in all patients. All patients had pre- and post-stimulation prolonged interictal scalp EEG recordings, including spike counts. Attention level was evaluated by means of the SNAP-IV questionnaire. The pre-implantation anti-epileptic drug regimen was maintained post-operatively in all patients.
Results: Post-operative CT documented that all electrodes were correctly located. There was no morbidity or mortality. Seizure frequency reduction ranging from 65 to 95% and increased attention level was seen in all patients. Interictal spiking frequency was reduced from 25 to 95%, but their morphology remained the same. There was re-synchronization of interictal discharges during slow-wave sleep in 2 patients.
Conclusion: All patients benefit from the procedure. The CM seems to play a role in modulating the epileptic discharges and attention in these patients. On the other hand, it is not the generator of the epileptic abnormality and appeared not to be involved in non-REM sleep-related interictal spiking modulation.

1. Introduction

The pathophysiology of both primary and secondary generalized epilepsy has been extensively discussed, but little consensus has been reached so far.[1] Lesional factors are extensively implicated in the development of secondary generalized epilepsy (SGE)[2] and genetic factors in the development of idiopathic primary generalized epilepsy (IGE).[3] The relative role of the corpus callosum, cortical and subcortical structures in the development and modulation of the disease has also been discussed.[4–7] Two major apparently contradictory theories (but not necessarily so) tried to explain the electrophysiological findings in generalized epilepsy: the centro-encephalic[8] and the cortico-reticular theory.[9] In summary, the centro-encephalic theory claims the existence of a central pacemaker, located in deep subcortical structures that would be the generator of the epileptic discharges registered at the cortical level. On the other hand, the cortico-reticular theory states that the epileptic activity was generated by an abnormal interaction between the neocortex and some of the subcortical structures mentioned by the centroencephalic theory.

Callosal sections have been used as a palliative procedure in the treatment of both IGE and SGE.[10–15] These consistent clinical findings suggested that cortico–cortical interaction was important in seizure generation in both SGE and IGE, but did not exclude a modulatory function of subcortical structures. In fact, many of these patients submitted to extensive callosal sections in whom post-operative EEG showed asynchronous hemispheric discharges (post-callosotomy rhythm) had re-synchronization of the discharges during sleep, suggesting that subcortical structures were indeed modulating cortical activity.

Deep brain stimulation (DBS) has been increasingly used in the treatment of refractory epilepsy over the last decade. Both subcortical (mainly thalamic) or supratentorial (hippocampus) structures have already been targeted.[16] The centro-median (CM)

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Table 1
Summary of the pre-operative clinical findings. IGE: idiopathic generalized epilepsy; SW: spike and wave; AT: atonic seizures; AA: atypical absence seizures; MYO: myoclonic seizures; TO: tonic seizures; TC: tonic–clonic seizures; TA: typical absence seizures; Sz: seizure; CS; callosotomy; Freq: frequency.

Patient	Age Sz onset	Sz types	Syndrome	Pre-CS Sz freq.	EEG at diagnosis
1	7	AT/AA/MYO/TO/TC	Lennox-Gastaut	Daily	Diffuse polispike
2	8	TA/TC	Lennox-like	Daily	Diffuse polispike
3	2	TA/TC	IGE	Daily	Diffuse SW 2.5 Hz
4	8	TA/TC	IGE	Daily	Diffuse SW 3.0 Hz

thalamic nucleus is a non-specific brain relay very likely related to the modulation of the epileptic activity seen in generalized epilepsy.[17] We report on the outcome after CM-DBS in patients with SGE and IGE who had been previously treated with extended callosal section and remained with frequent disabling daily seizures despite optimal medical treatment.

2. Methods

Four consecutive patients with generalized epilepsy who were previously submitted to callosal section and had at least 1 year of follow-up after deep brain implantation were studied. All patients were treated with at least high dose valproate, lamotrigine and phenobarbital in mono- or politherapy before surgery. All patients were previously submitted to extended callosal section, which consisted in a 90% callosal section, leaving only the splenium in place, in a single procedure. Details of this procedure have been published previously.[13] All callosal sections were documented by post-operative MRI. All patients were submitted to bilateral CM thalamic DBS. Under general anesthesia, a stereotactic frame was attached to the patient's head and stereotactic CT and MRI were acquired and fused whenever needed. The CM was targeted using proportional data in the AC–PC (anterior commissure–posterior commissure) space according to the Schaltembrandt atlas. A point located bilaterally at the level of the posterior commissural point (intersection of the posterior commissure and posterior perpendicular plane) and 10 mm lateral to the midline was chosen in all patients for the location of the more distal electrode of a quadripolar Medtronic Kinetra^{R} DBS device. The electrode was inserted through a burr hole located immediately in front of the coronal suture, 1.5 cm from the midline. An intra-operative scalp EEG was obtained and low (6 Hz, 4 V, 300 μs) and high-frequency (130 Hz, 4 V, 300 μs) stimulation was carried out. A generalized bilateral recruiting response prevailing ipsilaterally was seen after low-frequency unilateral stimulation and a bilateral DC-shift after high-frequency stimulation, in all patients. The electrodes were immediately connected to the generator in the same procedure and remained off until sutures were removed 21 days after implantation. Chronic continuous stimulation between the more proximal and distal contacts was carried out by progressive increments of 0.2 V in intensity every 2 weeks, until the final parameters (2 V, 130 Hz and 300 μs) were reached in all patients. Patients kept a seizure diary pre- and post-operatively. Post-operative CT scans documented the electrode position in all patients. All patients had pre- and post-stimulation prolonged interictal scalp EEG recordings (10–20 system), including manual spike counts and visual analysis of bilateral synchrony. Attention level was evaluated by means of the attention-related 18-questions of the SNAP-IV questionnaire[18] at baseline and 6 and 12 months after stimulation was started. A single question, using the same rating system, regarding verbal output was added, thus yielding a 19-questions tool (extended-SNAP). The pre-implantation anti-epileptic drug regimen was maintained post-operatively in all patients.

Statistical analysis was carried out using the Student *T*-test when needed.

3. Results

A summary of the patients' pre-operative clinical data can be seen in Table 1.

MRI was normal in three patients and showed moderate diffuse atrophy in one. Post-operative CT documented that all electrodes were correctly located (Fig. 1). There was no morbidity or mortality. Follow-up time ranged from 1 to 2 years after CM-DBS (mean = 1.5 years).

Age at CM-DBS ranged from 19 to 44 years (mean = 30.7 years). Mean age at seizure onset was 6.2 years (2–8 years). One patient had the diagnosis of Lennox-Gastaut syndrome, one of Lennox-like syndrome (some Lennox-Gastaut features but without an epileptic recruiting rhythm during slow-wave sleep) and two of primary idiopathic generalized epilepsy (IGE). The patient with Lennox-Gastaut syndrome had multiple seizures types including tonic, atonic, atypical absences, myoclonic and tonic–clonic seizures; the three other patients had simple absences and tonic–clonic seizures. All patients had daily seizures before callosal section. After callosal section, seizure frequency decreased from 65 to 95% in all patients, but all of them remained with daily absence and tonic–clonic seizures (Table 2). During CM-DBS, an additional decrease in seizure frequency ranging from 65 to 98% was noted in all patients (mean = 78%) (Table 3).

Before callosal section, EEG showed bilateral and synchronous spike-and-wave discharges (2.5–3.0 Hz) in two patients (those

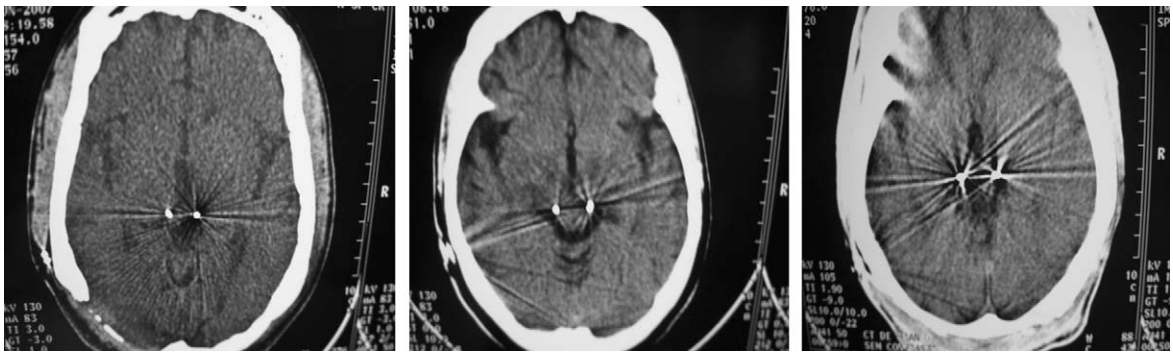

Fig. 1. Axial CT slices at the level of the posterior commissure showing the electrodes' tip (seen as white dots) position in three different patients.

Table 2
Summary of the clinical findings after callosal section. CS: callosotomy; Re-synch: re-synchronization; Sz: seizures.

Patient	Age at CS	Post-CS awake EEG	Sleep EEG re-synch	Post-CS Sz freq.	Post-CS Sz reduction
1	14	No synchrony	Yes	Daily	80%
2	40	No synchrony	No	Daily	95%
3	30	No synchrony	No	Daily	80%
4	23	No synchrony	Yes	Daily	65%

Table 3
Summary of the clinical findings during CM-DBS. F-U: follow-up; Sz: seizures; Freq: frequency; Re-synch: re-synchronization.

Patient	Age at DBS	F-U DBS	Sz freq DBS	Sz reduction DBS	Sleep EEG re-synch	Spike decrease DBS	Spike morphology DBS
1	19	2 years	Rare	98%*	Yes	99%*	Unaltered
2	44	2 years	1×/week	65%*	No	60%*	Unaltered
3	36	1 year	3×/week	70%*	No	90%*	Unaltered
4	24	1 year	5×/week	85%*	Yes	25%	Unaltered

* Statistically significant.

with the diagnosis of IGE), diffuse secondary bilateral synchrony in one (with Lennox-Gastaut syndrome) and diffuse polyspikes in one (with Lennox-like syndrome). After callosotomy, rupture of bilateral synchrony was seen in all patients; spikes could be seen independently over each hemisphere. In two, there was re-synchronization of the discharges during slow-wave sleep. Re-synchronization of the discharges persisted during DBS in these two patients. A decrease in the interictal spike frequency of appearance was noted in all patients during CM-DBS and ranged from 25 to 99% (mean = 68.5%). Pre-CM-DBS spike frequency/hour was 300, 120, 150 and 180 in patients 1–4, respectively, compared to 3, 48, 15 and 135 during CM-DBS, respectively. The morphology and spatial distribution of the interictal spikes were unchanged during CM-DBS (Fig. 2).

A clinically relevant increase in attention level was noted in all patients during DBS, as documented by improvement of at least one point in a mean of 9 items (ranging from 8 to 13 items) in the extended SNAP-IV questionnaire. The improvement in attention level was noted always prior to the decrease in seizure frequency in these patients; attention started to improve when stimulation reached 0.5 V of intensity, while seizure frequency decrease was noted only after intensity reached at least 1.2 V. There was

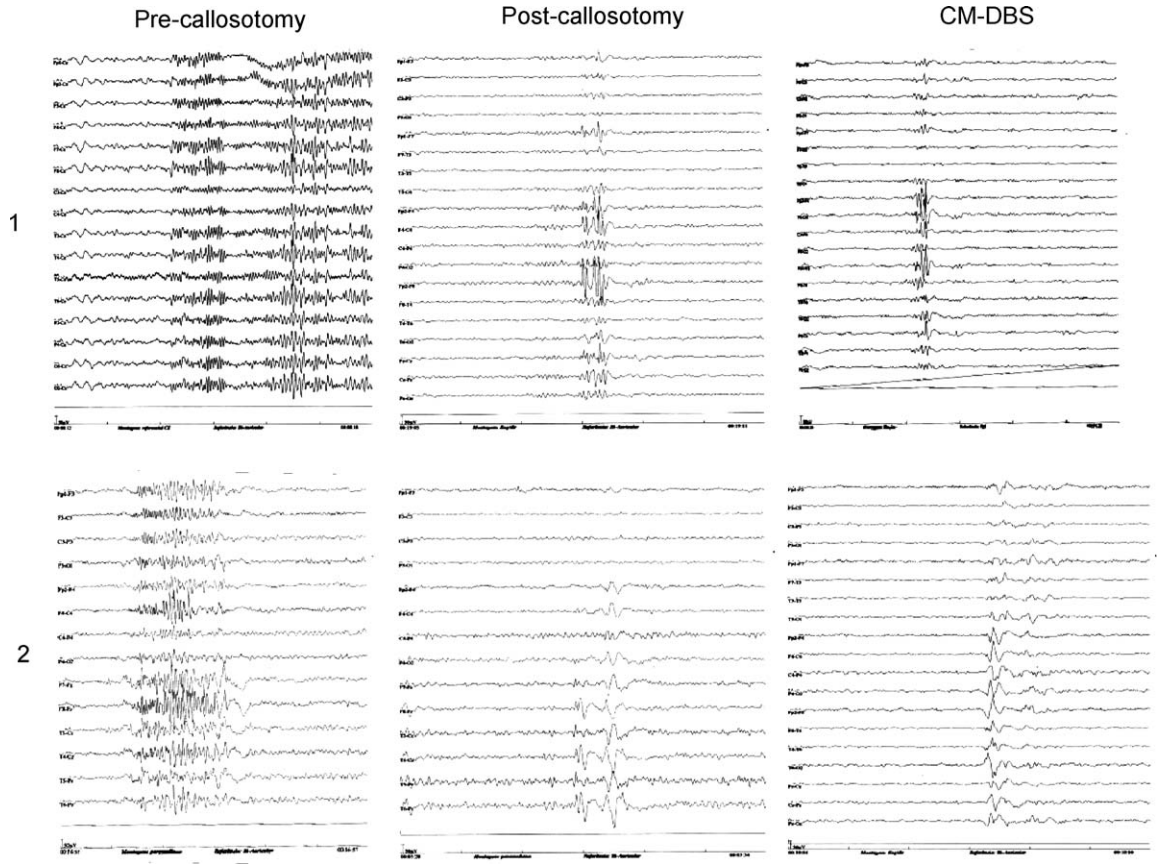

Fig. 2. EEG samples obtained from two different patients (1 and 2). The recordings on the left were obtained before callosotomy was performed (pre-operative basal findings); tracings in the middle show post-callosotomy EEG findings and those on the right were obtained during CM-DBS. Diffuse bilateral and synchronous discharges could be seen before callosal section. After callosotomy, spike frequency of appearance decreased. During DBS, an additional decrease in spike frequency of appearance was noted, but their morphology and distribution pattern remained similar to that seen before stimulation.

Table 4
Cognitive findings during CM-DBS. Pre-CS: pre-callosotomy; post-CS: post-casllosotomy.

Patient	Attention improvement	Pre-CS IQ	Post-CS IQ	Post-DBS IQ
1	10 out of 19 SNAP-IV items	62	64	68
2	5 out of 19 SNAP-IV items	94	95	98
3	8 out of 19 SNAP-IV items	76	79	85
4	13 out of 19 SNAP-IV items	77	79	82

progressive seizure frequency reduction up to the final 2.0 V stimulation level.

Mean general IQ was 77 (62–94) before and 79 (64–95) after callosotomy. After 1 year of CM-DBS, mean general IQ was 83 (68–98) (Table 4).

One patient (patient 3) received vagus nerve stimulation therapy after callosotomy and before CM-DBS without any clinical improvement.

We did not observe any side-effect related to bilateral thalamic stimulation, although some patients presented with short-lasting (15–20 min) contralateral paresthesia immediately after each voltage increase beyond 1.0 V.

4. Discussion

This series is the first one to report the outcome after CM-DBS in patients with generalized epilepsy previously submitted to callosal section. Stimulation of the centro-median thalamic nuclei was effective in reducing generalized seizure frequency by 25–98% as noted by others[19] and in increasing attention in our series. Although there was seizure frequency reduction in all patients, the most striking clinical finding was increased attention level. All patients had increased verbal output; it is not clear how much of this higher verbal output was related to increased attention level alone. The anti-epileptic drug regimen was kept the same during CM-DBS and cognitive improvement was very unlikely related to AEDs plasma level modifications.

Increased attention level has also been seen in other patient populations in whom seizure frequency was dramatically reduced, such as after cortical resection or callosal section.[20] This improvement in attention level has been rarely documented, possibly due to the lack of adequate tools to measure attention. This is particularly so in patients with diffuse cognitive deficits, as is very often the case in patients with generalized epilepsy. The SNAP questionnaire seemed to be useful and was able to document attention level improvement after DBS that correlated well to better daily life performance.[21]

All our patients were previously submitted to extended callosal section. This procedure led to rupture of secondary bilateral synchrony (SBS) in all of them, suggesting that the corpus callosum was a relevant brain relay in the genesis of the abnormality. SBS rupture correlated well to clinical improvement in these patients. Stimulation of the CM thalamic nuclei led to lower seizure frequency and 25–99% interictal spiking reduction as well. On the other hand, the morphology and topographical distribution of the residual spikes did not differ from those before stimulation. Additionally, two of our patients continue to disclose re-synchronization of EEG interictal discharges during sleep, which was already present after callosotomy. These findings favor the idea that CM might modulate the epileptic activity in these patients but does not represent a main structure involved in the generation of the epileptic abnormality. CM stimulation inability to avoid re-synchronization during sleep also suggest that this nucleus might not be actively involved in the mechanisms underlying the sleep-induced modifications in epileptic activity that has been previously recognized both in focal and generalized epilepsy.[22]

On the other hand, CM appeared to be intimately involved in the mechanisms related to sustained attention in these patients. Although it could be argued that increased attention level might had correlated to seizure frequency reduction alone, improvement in attention was so marked in all patients according to their family or caregiver, that a putative role of CM in it might be postulated. Additionally, the improvement in attention level was noted at lower stimuli intensity as compared to seizure frequency reduction, which might also suggest a specific role of CM in attention mechanisms. Actually, the non-specific character of this nucleus might favor a more widespread action upon the cortex. CM stimulation using the present parameters is very likely to cause local and passing fibers tracts inhibition, although the overall response in other nuclei is still unknown.

Unilateral effects were not seen during CM-DBS. This might be related to the fact that we were performing bilateral continuous thalamic stimulation and not unilateral stimulation. On the other hand, the fact that acute intra-operative unilateral stimulation of the CM always yielded bilateral responses might postulate that unilateral CM stimulation would be as effective as a bilateral one, but this has never been tried.

No patient presented somnolence or increase in interictal epileptic discharges; we were unable to trigger characteristic spike-and-wave discharges with low-frequency stimulation of the CM. As far as stimulation parameters were kept stable, clinical response was stable too and did not improve in time, as might happen with other types of modulatory treatment, such as vagus nerve simulation, suggesting a direct effect of CM stimulation in seizure and attention modulation.

The presence of recruiting responses and DC-shifts has been used to confirm the adequate position of the electrodes at the CM by some authors.[23] We were able to replicate these observations, but identical findings could also be obtained after stimulation of other thalamic nuclei, such as the anterior nucleus[24] (Cukiert, personal communication). These neurophysiological responses did not seem to be specific and they were probably inadequate as a localizing tool during implantation. On the other hand, it could be used as an intra-operative test for hardware and connections performance. Microelectrode recording characterization of the CM activity, currently under way in our center, would be needed to further refine the targeting technique.

One of our patients had a definite diagnosis of Lennox-Gastaut syndrome and happened to be our best clinical result. The other three did well, but not as much as the first one. It is yet not clear if this was a random excellent response to treatment or if this better response is related to the diagnosis of Lennox-Gastaut syndrome itself.

All patients with generalized epilepsy in our center who are currently undergoing CM-DBS were previously submitted to callosal section. It is not possible to elaborate on the relative efficacy of both callosotomy and DBS at this point. On the other hand, VNS has yielded poor results in this very refractory patient population. Clearly, patients who were previously submitted to callosal section or VNS benefit from CM-DBS in this series, although the open-labeled, uncontrolled nature of the present report should be considered. Extending our thalamic DBS series would enable us to further understand its role in seizure frequency

modulation as well as its role in higher cortical functioning and attention.

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