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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

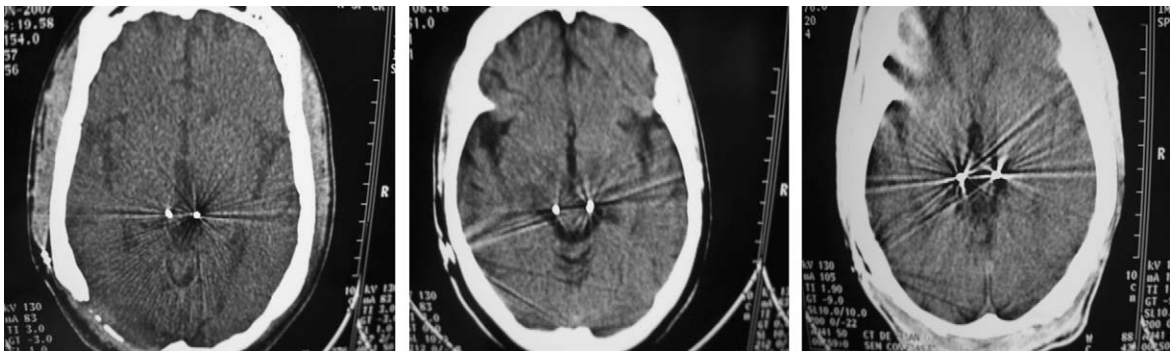

Fig. 1. Axial CT slices at the level of the posterior commissure showing the electrodes' tip (seen as white dots) position in three different patients.