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# NEUROMODULATION OF EPILEPTIC FOCI IN PATIENTS WITH NON-LESIONAL REFRACTORY MOTOR EPILEPSY

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We report two cases of chronic therapeutic stimulation of epileptic foci localized in motor areas. Case 1 is an adolescent with supplementary motor area seizures whose intracranial recordings showed a right SMA focus. Case 2 is a female teenager with primary motor seizures originating in the right motor cortex in the hand area as shown by her intracranial recordings and cortical mapping. Both had apparently normal MRI. Chronic stimulation of the epileptic focus decreased the number of seizures more than 90% the seizure number while preserving motor function. None of the patients had side effects. Neuromodulation is proposed as a safe, efficient surgical alternative for motor seizure control.

*Keywords*: Extratemporal epilepsy; motor seizures; motor cortex stimulation; neuromodulation.

## 1. Introduction

When one thinks of epilepsy surgery, temporal lobectomy immediately comes to mind. Temporal lobectomies constitute more than half the surgical procedures in major Epilepsy Surgery Clinics, including ours. (Velasco *et al.*,[34] Schuele & Lüders,[27]). But even though surgery outside of the temporal lobe for focal epilepsy accounts for less than half of all epilepsy surgeries, such procedures have tended to increase thanks to modern imaging studies, new surgical techniques, and more patient awareness of the possibility of having epilepsy surgery.

Traditional ablative procedures include lesionectomies, which render total seizure control in 57% of patients; lobectomies, which result in 26% seizure free patients, 30% with partial improvement and neurological deficit (paresis, conduct disturbances) (Olivier,[24,25] Villemure[35]). Multiple subpial resections according to Morrell,[20] render 55% seizure free patients, but Conolly *et al.*[8] reports neurological deficit such as permanent hemiparesia, hemiplegia and mutism with this procedure. Tailored epileptic focus resection, that is, to resect the area that is producing the epileptic activity regardless of whether such tissue is part of the imaged lesion or not is another alternative, nevertheless, different centers report 22–30% seizure free patients with 20–50% non significant or no improvement at all (Cascino *et al.*,[7] Olivier[25]). When the epileptic focus is localized in the extratemporal cortex with no lesion at all demonstrated in MRI, the seizure outcome is even poorer with recurrence in 75% of the few responding patients (Asztely *et al.*,[3] Jeha *et al.*,[16] Kim *et al.*,[18]).

Since the goal of epilepsy surgery is to eliminate seizures without causing neurological deficit, epilepsy surgery in patients with seizures originating in motor areas constitutes an important problem epileptologists have to deal with, especially because there is a high risk of neurological sequelae as explained above. Therefore, a non-ablative surgical method is desirable; neuromodulation could be an alternative in these cases.

Neuromodulation for intractable seizures has been applied in different targets: centromedian (Velasco *et al.*,[30] Velasco *et al.*[33]) and anterior

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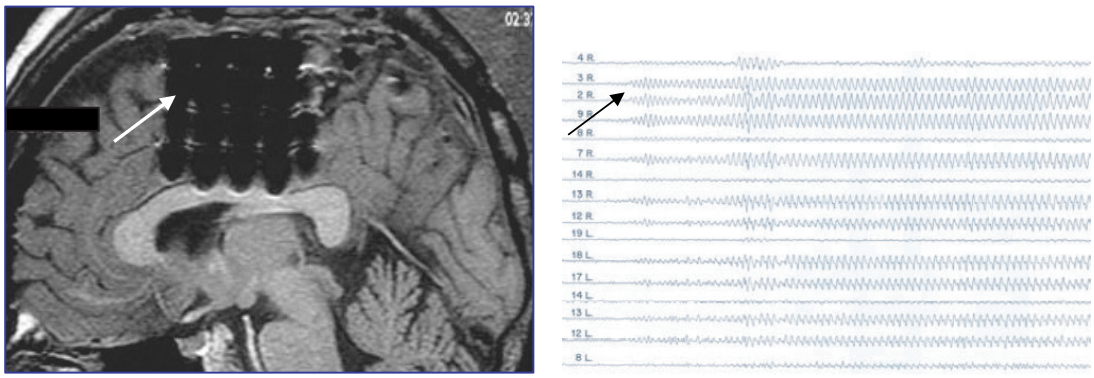
thalamic nuclei (Kerrigan *et al.*[17]), cerebellar (Cooper *et al.*,[9] Davis & Emmans[12] and Velasco *et al.*[32]), vagal stimulation (Morris & Mueller,[21] Frost *et al.*[15] and Amar *et al.*) and hippocampus (Velasco *et al.*,[31] Tellez-Zenteno *et al.*,[28] Velasco *et al.*,[34] Boon *et al.*[6]). Direct stimulation of frontal lobe foci represents a novel approach to treatment of intractable seizures for which only one previous case report exists (Elisevich *et al.*[14]). The purpose of this preliminary report is to analyze the efficacy and safety of electrical stimulation of the epileptic foci in frontal motor areas in two patients with no lesion observed by MRI and followed for 18 months.

## 2. Data and Methods

The study was approved by the Ethical and Research Committees of the General Hospital. Patients and family signed informed consent. Two patients were included, one with supplementary motor area and one with primary motor area seizures. As part of the Epilepsy Surgery Clinic protocol these patients underwent a 6 month follow-up prior to surgery. During this time, serial EEGs and MRI were performed; correct antiepileptic drug therapy compliance was assured and therapeutic blood levels were verified; patient and caregiver were trained to have an adequate seizure count and thus reliable seizure diaries. Psychiatric evaluation for behavioral disturbances and family integration problems was performed. Three months before diagnostic electrode implantation, patients underwent neuropsychological testing. A wide battery of tests was performed to evaluate patients' mental status. To study language dominance, the dichotic listening test (Kimura,[19] Voyer[36]) validated for Spanish speaking patients (Azañón-Gracia 2005) was used. The testing batteries for the patients included the Neuropsi Attention and Memory Battery (Ostrosky-Solis *et al.*,[26]) which is a comprehensive battery developed for evaluating attention, memory, and executive functions. The tests have been standardized and validated in Spanish-speaking subjects from 6 to 85 years of age and designed to utilize different items in subsequent examinations to avoid learning. Scores are corrected according to age and education. Subtests are organized into summary index scores that yield a Total Attention and Memory Index score, as well as separate scores for Attention and Memory Processes. In this evaluation we emphasized total attention and executive functions scores that included level of alertness, span or efficiency of vigilance–concentration, and selective attention. For the executive functions assessment: concept formation, flexibility, inhibition and several motor programming tasks such as the go–no go task and assessment of motor perseveration were utilized.

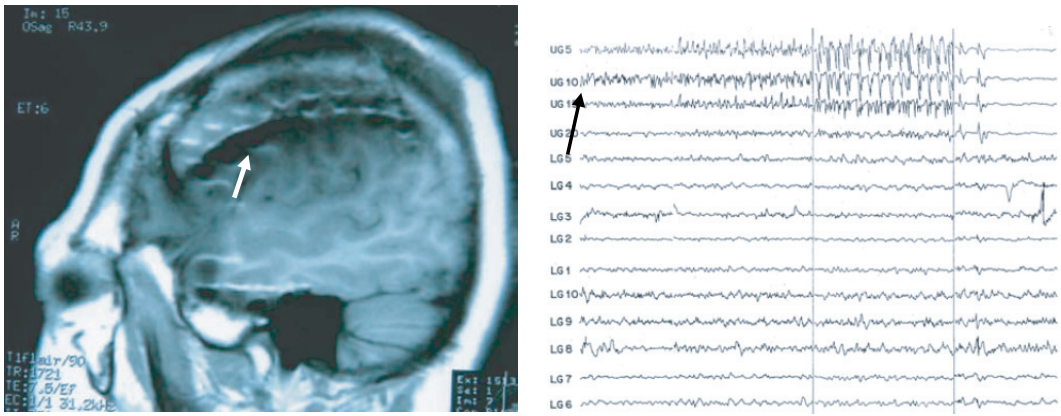
The Quality of Life in Epilepsy Inventory (QOLIE) for adolescents (Cramer *et al.*[10]) was administered and accurate seizure calendars were recorded. Patients were hospitalized at the start of phase II of the Epilepsy Surgery Clinic Protocol, which consists of subdural grid implantation over the cortical area where clinical data and surface EEG recordings indicated the seizure onset (Fig. 1(a) and 2(a)) to localize the precise site of focus. Grid position was confirmed with MRI scans of implanted grids, antiepileptic drugs were tapered and monitoring started.

Case 1: A 17-year-old male whose seizures started three years earlier was studied. His ictal events were characteristic supplementary motor seizures, that is, brief, with abrupt posturing of left arm and sudden version of the head to the left, followed by clonic movements of left hand, and occasionally, secondary tonic clonic seizures. Consciousness was preserved unless seizures became generalized. Family complained because the patient had behavioral abnormalities with perseverance and verbal aggressiveness. In his physical exam, several scars on his face and head were observed (due to multiple falls caused by seizures). Even though his performance in the neuropsychological tests was normal, examiners agreed on perseverance, and personal interviews showed his aggressive attitude. He had failed multiple drug trials and his current medication was the one which rendered better results: phenytoin 300 mg, valproate 3000 mg and levetiracetam 3000 mg per day. Surface EEGs showed frontal parasagittal epileptic activity with phase reversal in frontal midline, from which no laterality could be determined. MRI was normal. Bilateral 20 contact grids were implanted in right and left SMA (Fig. 1(a)) through a $7 \times 5$ cm craniotomy allowing the *dura* to be opened on both sides of the sagittal sinus, between the coronal suture and the vertex. Daily depth recording was performed without AEDs; interictal and ictal EEG activity showed a mesial focus located in the contacts 3, 2




(a) (b)

Fig. 1. Case 1, patient with supplementary motor cortex epilepsy. 1(a) shows MRI with right 20 contact grid position; white arrow indicates contacts 3 and 9 where ictal activity initiated. 1(b) shows ictal recording, black arrow indicates seizure onset on right grid contacts 3R and 9R.




(a) (b)

Fig. 2. Case 2, patient with primary motor cortex seizures. 2(a) shows MRI with right 20 contact grid position; white arrow indicates contact UG10 where ictal activity initiated. 2(b) shows ictal recording, black arrow indicates seizure onset on contact UG10 (upper frontal grid). Vertical lines show where recording was cut, for space purposes.

and 9 of the right SMA grid (Fig. 1(b)). Cortical stimulation through the grid in these contacts produced posturing of the left arm, with version of the head to the left.

Case 2: A 17 year old female who started having seizures at 5 years of age. Her seizures started with a sensory aura consisting of dysesthesia localized in her left hand (creating a cramp sensation), afterwards she had left hand clonic movements that propagated to the left leg and left side of her face with secondary tonic clonic seizures. Consciousness was preserved unless secondary generalized seizures ensued. After the seizure there was left face and left corporal paresis (Todd's phenomenon). Her family also described episodes characterized by prolonged behavior arrest and eye blinking. EEG showed non localizing slow activity and she had a normal MRI. Neurological exam showed a paresis in the left arm. She had behavioral abnormalities with perseverance and aggressiveness. Her neuropsychological tests showed mental retardation with an IQ of 59 according to the Weschler[37] Intelligence Scale Revised for Scholar level (Spanish-WISC-R) with severe abnormalities in her attention and executive performance. She had failed trials with several antiepileptic drugs.

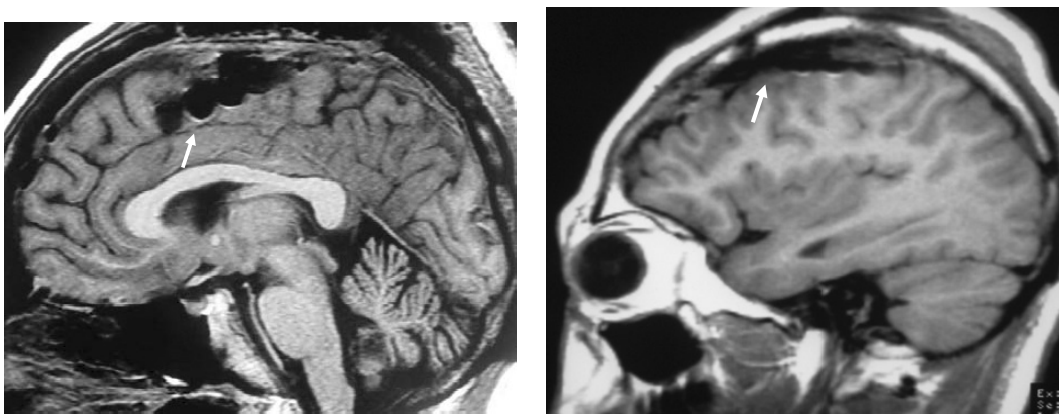
Current medication was carbamazepine 1200 mg per day and primidone 750 mg per day. Three 20 contact grids were implanted (Fig. 2(a)): two in the right sensory-motor area to be able to record from hand, face and a leg area, the other was a right temporal grid. Daily depth recording was performed without AEDs and ictal EEG activity showed the epileptic focus localized in contact 10 of the upper frontal grid (UG10) (Fig. 2(b)). Stimulation of this area provoked movements of the left fingers and hand.

Once the epileptic focus was localized, patients were reinitiated on AEDs. Diagnostic grids were explanted and replaced with permanent four contact electrodes for chronic stimulation (Resume, Medtronic, Inc., Minneapolis, MN, USA). Diagnostic electrodes were used as guides to implant permanent electrodes for brain stimulation, directing the latter to the epileptic focus so that a contiguous pair of the permanent four contact electrode would be right over the epileptic focus. MRI was used to confirm electrode position (Figs. 3(a) and 3(b)). Afterwards, a pulse generator for chronic stimulation (ITREL II by Medtronic Inc., Minneapolis, MN) was implanted in the thorax and connected through a low profile extension to the intracranial electrode. Parameters for electrical stimulation of the motor cortex included the following: trains consisted of 130 Hz biphasic pulses of 450 $\mu$sec duration with amplitude of $< 450\,\mu$A. Using these parameters limited charge density within safety limits (Babb *et al.*,[4] Ebner *et al.*[13]). The charge density for these parameters is $< 3.0\,\mu$C/cm2/phase according to the formula described by Velasco *et al.*[32]:

$$\text{Charge density}(\mu\text{C/cm2/phase}) = \frac{\text{amplitude(mAmp)} \times \text{pulse width(ms)}}{\text{cathodal electrode area (cm}^2\text{)}}$$

Although Patient 1 initially received continuous stimulation, the battery showed rapid depletion, so continuous stimulation was changed to a cyclic stimulation mode on month 11, with no apparent change, since the patient continued to be seizure free. Nevertheless, by month 18 seizures started to reappear, the battery had depleted. The patient could not have an immediate replacement due to economic problems; although seizures increased, they only reached 40% of the baseline number. The pulse generator was replaced 8 months later and seizures decreased again so that by the end of the first month, they had disappeared again. Cyclic stimulation (1 minute ON/4 minutes OFF) has been used for centromedian thalamic neuromodulation (Velasco *et al.*,[30] Velasco *et al.*[33]) with the idea of preventing tissue damage. It has shown good antiepileptic effect and has the advantage of prolonging the battery life span. Afterwards the cyclic mode was also used instead of continuous mode in hippocampal stimulation for mesial temporal lobe epilepsy (Velasco *et al.*[34]) maintaining the same effectiveness in seizure reduction.

Patient 2 had a cyclic mode from the beginning of her stimulation and the battery has shown less depletion. The cyclic mode used in both patients



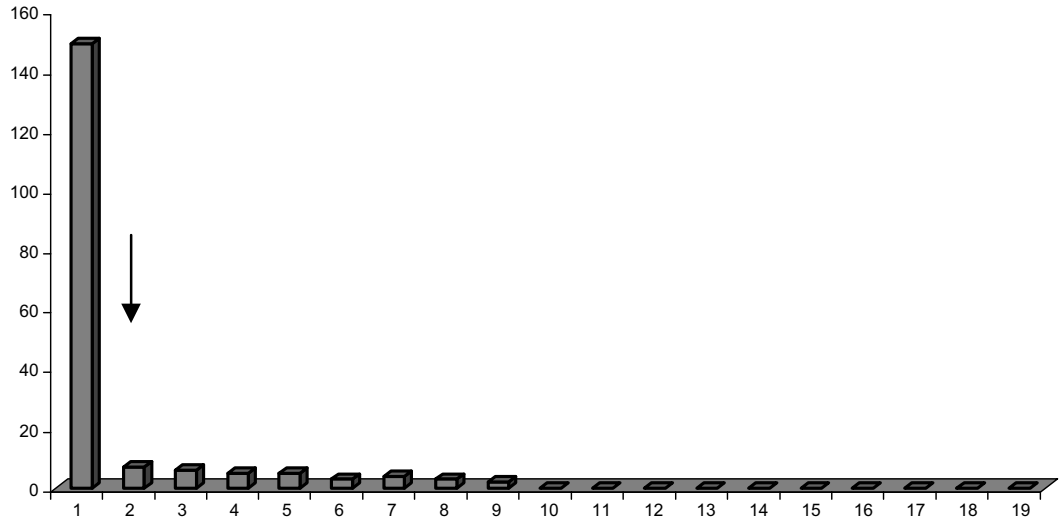
(a) (b)

Fig. 3. MRI showing definite therapeutic 4 contact electrode position. 3(a) shows Case 1 electrode within the supplementary motor area. 3(b) shows ase 2 electrode position within the motor cortex. The permanent 4 contact electrode is implanted using the diagnostic grid that is removed in the same surgical procedure as a guide. The chronic stimulation contacts must overlap the epileptic focus area. White arrows indicate pair of stimulated contacts in both patients.

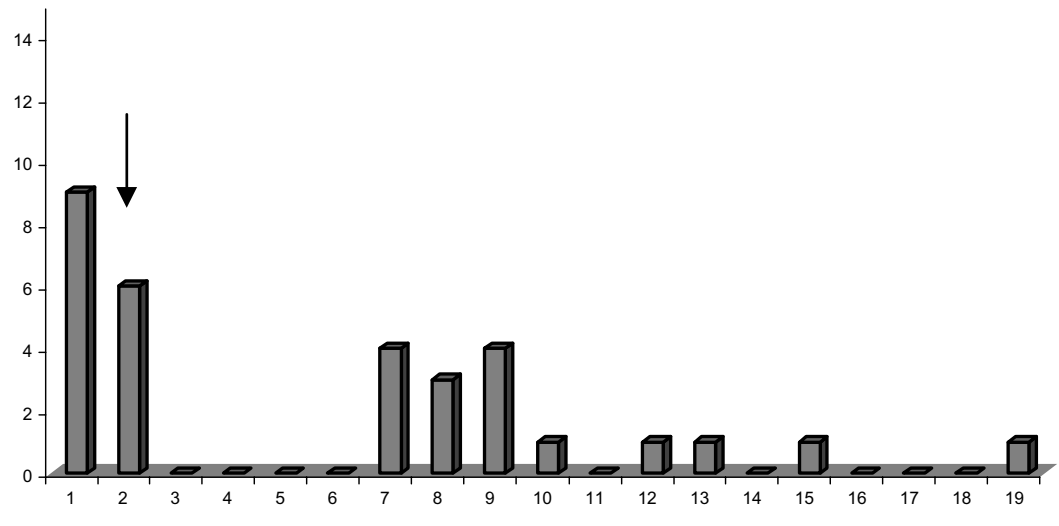
consisted of 1 min trains of square biphasic pulses with a 4 min *interstimulus* interval. Follow-up was performed in both patients at 3–6 and 12 months with seizure count, EEG, neuropsychological tests to evaluate performance and QOLIE scales. An additional follow-up visit at month 18 was included.

## 3. Results

All surgical procedures were well tolerated by both patients. Neither edema nor hemorrhages were present. Both patients were unaware when the pulse generator was on or off, as there were no symptoms when it was on. Up to the present date, there have been no skin erosions or other problems related to system implantation.Both cases experienced seizure reduction, both in number of seizures and in severity of each seizure. Case 1 went from 150 spontaneous seizures per month to 4 seizures per month from the first month of stimulation (Fig. 4(a)). The initial response for Case 2 was retarded because we started stimulation at pulse amplitude (250 $\mu$A) to avoid any




(a)




(b)

Fig. 4. Graphs showing seizure counts per month. 4(a) corresponds to Case 1, 4(b) to Case 2. In both graphs the first column is the one month baseline count and thereafter, each bar corresponds to 12 consecutive months of neuromodulation therapy. Arrows indicate neuromodulation onset. Note that by month 11, both patients were seizure free.

possible side effects of stimulating primary motor cortex. We gradually increased intensity to 350 $\mu$A and achieved 3 months with no seizures. On months 6, 7, 8 and 9, the patient had a few very brief clonic movements and amplitude was increased to 400 $\mu$A and the patient has been 4 months seizure free (Fig. 4(b)). Follow up EEGs performed at months 3, and 6 showed gradual decreases in spike counts and by month 12 spikes were absent. Case 1 remained seizure free from month 11 until month 18 and case 2 showed occasional brief partial seizures localized to the hand with no propagation or Todd's phenomenon during the same period of time.

Neuropsychological testing in Patient 1 showed that his normal status was maintained with no decreased in performance in any subscale. His perseverance stopped and he was more tolerant showing no aggressive bursts. Patient 2 had severe abnormalities in her baseline tests prior to surgery and although she continues to be in severe range of abnormality, she has shown improvement in all subscales.

Table 1 shows the QOLIE for both patients three months before starting chronic electrical stimulation (PRESTIM) and one year after chronic electrical stimulation (1 YEAR STIM), as well as the difference between both to demonstrate the degree of change. Both patients improved in the global scale, but Case 2 had a much better improvement (33 points vs Case 1: 17.56 points).

## 4. Discussion

Several groups that perform neuromodulation in epilepsy have commented on the safety issue. In comparison to surgical removal of epileptic tissue, neuromodulation has proven to be safe and this was the case with our patients. Both of them tolerated surgical procedures *per se* since electrode implantation itself is less invasive than craniotomy and tissue ablation; thus no complications were present such as those reported by Cascino *et al.*[7]: infection, hematomas and subdural collections. These complications of ablative surgery left permanent deficits, often needed a second surgical procedure to correct them and all patients had to undergo rehabilitation. In addition, stimulated patients in the current report were also free of undesirable effects due to the stimulation system presence since none of them had skin erosions as reported in earlier studies Velasco *et al.*[33,34]; Oh[23]; and Blomstedt.[5] This may be due to the use of low profile extensions. Patients were unaware if the stimulator was On or Off and had no postsurgical neurological deficit. This scenario is very different than conventional ablative surgery where neurological sequelae are frequent and sometimes severe. Elsevich *et al.*[14] reported a patient who underwent chronic stimulation of the epileptic focus localized in primary motor cortex for 5 years No side effects had been observed.

A reduction in number of seizures was observed in both patients though the decrease rate was different. In Patient 1 the effect was immediate, though a few breakthrough seizures continued to appear occasionally until month 10. From then on, the seizures disappeared.

As mentioned in the Results section, Patient 2 had a slower response than Patient 1. The reasons for

Table 1. Scores of QOLIE subscales and total scores are shown for Case 1 and Case 2. Prestim is the baseline with no stimulation test and 1 year stimulation is the follow-up QOLIE scale for one year stimulation therapy. Note the improvement in both patients, particularly in Case 2.

| SUBSCALE | Case 1 | | | Case 2 | | |
|---|---|---|---|---|---|---|
| | PRESTIM | 1 YEAR STIM | DIF | PRESTIM | 1 YEAR STIM | DIF |
| IMPACT | 8.4 | 12.27 | 3.88 | 7.75 | 19.73 | 11.98 |
| MEMORY | 0.39 | 8.5 | 8.11 | 4.68 | 12.33 | 7.65 |
| FUNCTIONING | 5.63 | 5.4 | −0.23 | 3.15 | 5.4 | 2.25 |
| STIGMA | 6.5 | 10.11 | 3.61 | 0.72 | 7.95 | 7.22 |
| SUPPORT | 0 | 0.88 | 0.88 | 0.5 | 0.83 | 0.33 |
| SCHOOL | 6 | 6 | 0 | 3.75 | 5.63 | 1.88 |
| ATTITUDES | 1.69 | 0 | −1.69 | 0.56 | 2.25 | 1.69 |
| HEALTH | 7 | 10 | 3 | 6 | 6 | 0 |
| Total | 35.59 | 53.16 | 17.56 | 27.11 | 60.11 | 33 |

this difference in response are not completely clear. The initial stimulus amplitude was low for two reasons, one was to obtain a seizure reduction with the least stimulus amplitude to be able to preserve battery life, and the second was for safety since we have never previously stimulated primary motor cortex for seizure control. An additional factor in Case 2 was that the stimulation was on a cyclic mode from the beginning since we had already observed that it worked in Patient 1 and that the stimulation effect took longer to appear. The third reason could be that the response was different because the stimulated area was different, though both are motor cortices, one is supplementary and the other is primary.

Even though 2 patients is a small number to draw strong conclusions, the seizure decrease is consistent with other studies that have used neuromodulation as a surgical alternative for seizure control. The prompt decrease observed during the first month of stimulation is similar to the one that is found in patients with mesial temporal epilepsy with no hippocampal sclerosis in whom stimulation of the hippocampus foci is performed (Velasco *et al.*[34]). When patients had hippocampal sclerosis, the seizure decrease took place after more than 6 months of chronic stimulation and was not sas significant. The two patients we present here had no evidence of structural lesion in their MRI scans; currently, we cannot tell if chronic stimulation of the motor cortex with MRI evidence of lesion will have the same result.

Several authors (Asztely*et al.*,[3] Jeha *et al.*,[16] Kim*et al.*[18]) have observed that 75% of those nonlesional patients who responded well to ablative surgery of motor cortex had seizure recurrence. In Elisevich's case report (Elisevich *et al.*,[14]) there was an initial seizure decrease, which not only had persisted after several years, but the patient continued to show further seizure reduction. It will be interesting to observe if this effect is maintained in our patients with neuromodulation and seizures do not relapse as reported in other type of epilepsy surgery.

Case 1 has had a longer follow-up during which the internalized pulse generator became depleted is interesting since it confirms the observation described in several neuromodulation studies for epilepsy in other targets (cerebellum, hippocampus, thalamus). Velasco *et al.*[33] presented follow-ups of three patients up to 45 months, which describe this observation. There is a carry-on effect after stimulation is stopped. This fact has also been shown in experimental studies in kindled rats in which hippocampus is stimulated at high frequency to stop seizures (Wyckhuys *et al.*[38]). This suggests that neuromodulation could induce plastic changes in stimulated tissue.

Our other main concern was function preservation. No adverse effect on motor function was observed. This is consistent with Elisevich's previous case (Elisevich *et al.*[14]) that was stimulated for more than 5 years without evidence of motor deficit. Even though these three are the only cases of chronic stimulation of the motor cortex for epilepsy, therapeutic chronic stimulation of this area has been performed in patients with intractable central pain without producing motor deficit (Tsubokawa[29], Nguyen *et al.*[22]). Even though the neuropsychological tests have different scores in both patients, Case 1 maintained his pre-stimulation scoring, which was within normal ranges. Case 2 had mental retardation and thus scores were low in the baseline period, but she maintained her scores and even showed a slight improvement. None of the patients showed motor deficit. We observed other areas that improved which were not evaluated, for example, a decrease in aggressive behavior, and Case 2 wanted to lose weight and improve her personal appearance. We need to apply other tests to evaluate not only function but also emotional changes.

Both patients perceived that their quality of life had improved and this is reflected in the QOLIE scales. It is worthwhile to mention that Case 2 had a higher improvement in her quality of life regardless of her low cognitive performance. This improvement could be the result of seizure number decrease but also to future expectations, with higher hopes that seizures can disappear.

There are some studies that have shown evidence that neuromodulation works by inhibiting the stimulated area. Clinical studies (Velasco *et al.*[31], Cuéllar-Herrera *et al.*[11]) using neurophysiologic testing, single positron emission tomography, and benzodiazepine receptor binding studies, showed that an inhibitory mechanism could explain seizure control. Basic studies provide similar evidence. Wyckhuys *et al.*[38] used high frequency stimulation of the hippocampus in kindled rats finding an increase of

afterdischarge thresholds as well as seizure reduction. This is a preliminary report that needs to be supported further with added paradigms to be able to explain the mechanism of action.

These two cases had the epileptic focus localized within 2 contacts of the recording grid. This allowed us to replace the grids with a single permanent 4 contact electrode. Nevertheless, we can foresee the possibility of future problems regarding hardware. A single patient could have a larger, polymorphic epileptogenic area that would not be stimulated adequately with a linear 4 contact electrode or have multiple foci that would need several electrodes. Team work with biomedical engineers will be needed to be able to solve these challenges.

## 5. Conclusion

Even though the present report has a limited number of patients, results are encouraging since neuromodulation of motor areas appears to be a safe, reversible non-lesional surgical alternative which could control seizures and preserve motor function. These preliminary results are the basis of a larger study we are currently performing.

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