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Video-EEG Telemetry with Transcranial Magnetic Stimulation before Cortical Stimulation for Epilepsia Partialis Continua

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Abstract

Introduction Epilepsia partialis continua (EPC) refers to recurrent focal motor seizures that occur every few seconds or minutes for extended periods.

Methods We describe a case report of a 51-year-old man with refractory epilepsy who was admitted with debilitating right arm jerks as a potential candidate for surgery. Previous video telemetry showed left centro-parietal, low amplitude spikes suggesting epilepsy with left central origin.

Results Repetitive transcranial magnetic stimulation (rTMS) over the parietal area decreased his right arm jerks. Due to this result a chronic cortical stimulator was implanted in the central parietal region, and this greatly improved his symptoms.

Conclusion This patient with EPC's responsiveness to treatment with rTMS suggested a role for chronic cortical stimulation therapy. This significantly reduced his symptoms although there was some variation in this reduction over the five years of follow-up.

Introduction

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive, or synchronous neuronal activity, in the brain (Fisher et al 2005). Status epilepticus is a condition resulting, either from the failure of the mechanisms responsible for seizure termination, or from the initiation of mechanisms which lead to abnormally prolonged seizures. This condition can have long-term consequences, including neuronal injury, neuronal death, and alteration of neuronal networks, depending on the type and duration of seizures (Trinka et al 2015). The 2015 ILAE task force report on status epilepticus classes Epilepsia Partialis Continua (EPC) as a subclass of focal motor status epilepticus (Trinka et al 2015). EPCs, typically affect the hand and face, although other body parts may be affected, and occur every few seconds or minutes for extended periods, days to years. The focal motor features may exhibit a Jacksonian march. A Todd's paresis may also be seen in the affected body part (ILAE 2021). “Transcranial magnetic stimulation (TMS) is a form of focal, non-invasive cortical stimulation in which a focal electric current is induced in the cerebral cortex.” (Tsuboyama et al 2020). TMS, coupled with either electromyography (EMG) or electroencephalography (EEG), enables rapid measurement of the cortical excitation/inhibition ratio, which is pathologically shifted toward excess excitability in patients with epilepsy (Valentín et al 2008, Kimiskidis et al 2014, Tsuboyama et al 2020). In this case report repetitive TMS (rTMS) with EEG was used to demonstrate that focal cortical stimulation could improve a patient’s EPC symptoms and that therefore he would benefit from a long-term intracranial cortical stimulator (Valentín 2008).

Methods

A 51-year-old man with refractory epilepsy was admitted with debilitating right arm jerks as a potential candidate for surgery. The patient was born in 1964 at term as the younger of twins, he reported mild birth complications. He had mild learning difficulties and finished school aged 16. He then worked as fruit-machine engineer and driver. He had his first generalised tonic-clonic seizure aged 19. After starting carbamazepine, he was seizure-free until aged 42. He then developed right arm jerks, mainly in his

shoulder that were stimulus sensitive, brought on by touch or movement and could also involve his whole arm and his right leg, which led to falls. These progressively worsened and he was clinically diagnosed with EPC. An initial EEG revealed no abnormalities. After stopping anti-epileptic medication, he was admitted to intensive care with generalised tonic-clonic seizures (GTCS) and discharged the next day. Still without medication he was admitted a month later diagnosed with status epilepticus, aspiration pneumonia and pulmonary embolisms. An MRI showed hypoxic brain injury. Three months later a 3T MRI showed left-sided nodular sub-ependymal grey matter heterotopia adjacent to the trigone of left lateral ventricle. Carbamazepine 600mg twice a day, with topiramate 400mg twice a day, significantly decreased the frequency of the jerks. However, the jerks continued to be so debilitating and distressing that he expressed interested in surgical treatment. On video telemetry he was found to have left central and parietal spikes suggests focal seizures whilst he was asleep (Figure 1). Isolated jerks of the right arm were associated with a clear spike in the left parietal and central areas. However, several of the more major seizures, with jerking and abduction of the right arm, did not show any clear ictal change, probably due to motor artifact.

Figure 1 Video Telemetry Example

04:29:23 Patient in bed and EEG shows stage II sleep.

04:29:25 Jerks are seen in the EMG lead over right deltoid.

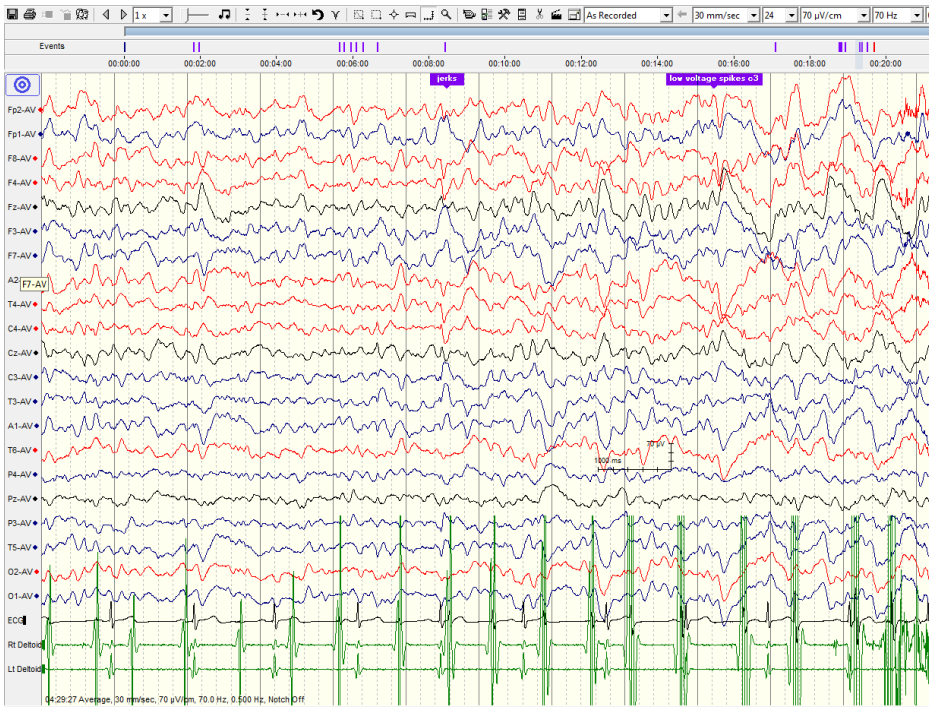
04:29:32 Some of these jerks, especially during sleep are associated with very low voltage left centro-parietal spikes (C3; P3)

04:29:38 Jerks become clinically visible with right hand twitches

04:29:39 Jerks become stronger, and he wakes up. Neck and shoulder jerks are now evident.

04:29:49 Tries to find the event button and presses it.

04:30:10 Jerks stop



Analysis with positron emission tomography (PET) showed reduced uptake in left parietal region. This was reported as a potential epileptic focus. He also underwent neuropsychology testing which reported he was functioning just below the borderline range of intelligence with higher non-verbal than verbal intelligence, possibly due to earlier hypoxic brain injury.

Results

The patient was referred to the TMS service as a potential candidate for cortical stimulation surgery and underwent video telemetry with rTMS.

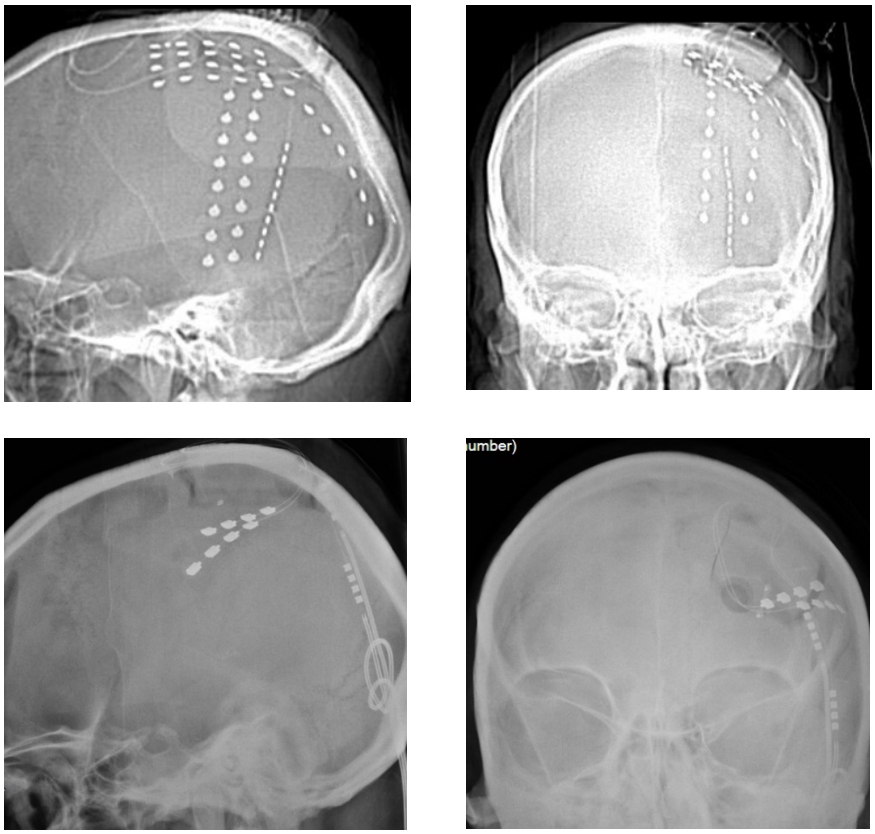
Video Telemetry with rTMS

The patient had multiple seizures brought on either by movement or touching of the right arm but usually without clear EEG change. Following rTMS over the parietal area 0.5 Hz, 750 pulses, he had a marked symptomatic improvement. No clear improvement was noted when stimulating over the left posterior frontal region. After stimulation he continued to have focal motor seizures with jerking on movement and touch but that appeared less severe. The effects lasted for two weeks and was considered an indication that chronic cortical stimulation might provide an effective long-term treatment.

Trial of Intracranial Electrodes

With the aim of further localising the epileptogenic focus, the patient was consented to undergo left partial craniotomy with electrode insertion. This was initially complicated by an extradural haematoma requiring clot evaluation and electrode removal later that day. One week later, he had subdural electrodes implanted over the posterior frontal and parietal regions (Figure 2) and had intracranial telemetry. A period of subacute cortical stimulation stopped the EPC when stimulating the primary parietal cortex over the hand area.

Figure 2 Electrode Positions



Two weeks later, two Medtronic Resume II 4-contact strip electrodes were inserted and positioned over the area previously covered by the inferior end of the grid and proximal end of the temporal strips. A clear improvement in the EEG and in the number of clinical seizures was noted, with clear improvement in the right arm function.

Follow-up Clinics

On follow-up at clinic, one month after the last surgery the stimulation intensity was decreased from 1.5mA to 1.3mA ov both sides for 450µs pulse duration, frequency of 130Hz because the previous intensity was associated with uncomfortable sensations in the left leg. When the stimulation was stopped, he had a typical arm jerk seizure and the leg sensation disappeared. The patient continued to take carbamazepine PR 600mg twice daily, topiramate 300mg in the morning and 350mg in the evening, and phenobarbital 60mg nightly. He reported a clear improvement in the right arm jerks since the cortical stimulators were implanted and he was able to pick up objects without evolving seizures.

At the clinic one month later, cortical stimulation was increased in the inferior cortical strip to 2 mA, with an immediate improvement in the arm and hand function without uncomfortable sensations in the leg. He was able to write his name and numbers for the first time in years without provoking clear arm jerks. However, he reported some earlier episodes of arm jerks lasting for several seconds. Some of these were thought to be related to a chronic weakness and it was suggested that arm exercises might help.

One year after the surgery stimulation intensity was increased to 3.5 mA at contacts 0+ and 3- and 3.1 mA at contacts 8+ and 11-. He continued to be able to write his name, though with some minor jerks resolving within 30 seconds. Three months later the patient reported two-week period with episodes of right sided jerking due to stimulator battery failure. This was replaced and his phenobarbital was also increased to 150mg at night. He had a clear improvement in the arm and hand function after replacing the battery. He was able to shake hands and move his fingers without any associated jerks.

One year and seven months after the surgery the patient hit the back of his head causing loss of consciousness for a couple of minutes, minor bone fracture and subdural haematoma. The EPC had returned when reviewed two months later after the trauma but with a slight improvement in severity the week before the clinic. There was no problem in electrode impedance. Phenobarbital was decreased to 60mg at night. Two months later stimulation parameters were changed to 3.2mA at contacts 1+ and 3- and 3.1mA at contacts 9+ and 11-. A month later phenobarbital increased to 150mg nightly. Six months later phenobarbital was decreased to 60mg, and he was noted to have no clear EPC periods during the months before the clinic.

The next yearly review showed he had no clear EPC periods during the preceding months. However, he did have some jerks on using his hand. On the most recent yearly review he described that after using his hand too much or writing his name he had jerks that either stopped after one minute or evolved to over an hour. Sometimes this facilitated jerking for 2-3 days.

Discussion and Conclusion

rTMS in conjunction with video telemetry assisted in the diagnosis and treatment of this patient by bridging the gap between initial clinical, EEG, PET and MRI evidence of parietal EPC and the chronic cortical stimulator implantation used as a long-term treatment. rTMS is a non-invasive technique that can terminate ongoing seizures, by interrupting neural activity and change cortical excitability, demonstrating the role for cortical stimulation. This report also demonstrates the risks of complications in surgical intervention with the subdural haematoma described above. Therefore, there is a utility in the use of non-invasive techniques like rTMS in future patients who are not suitable or do not desire the risks of surgery.

A PubMed literature search revealed five papers reporting nine patients with EPC treated by rTMS. Six patients had some reduction in their clinical seizures while three had no change. Of these patient's there were no significant side effects to the rTMS. However, this may not be representative of the true number of negative results for rTMS because of a potential reporting bias in the literature.

Table 1 (modified from Rotenberg et al (2009))

Reported in	Age	Aetiology	Coil position	rTMS intensity	rTMS frequency	Train duration	Number of trains	Outcome	Adverse events
Graff-Guerrero et al 2004	7	Unknown, focal cortical atrophy on MRI	Seizure focus	50% MO	20Hz	2s	15	Clinical seizures became intermittent and stopped in 24h	None reported
Graff-Guerrero 2004 et al	11	Unknown, focal cortical atrophy on MRI	Seizure focus	128% MT	20Hz	2s	15	No change in clinical seizures, improved EEG	None reported
Schrader et al 2005	48	Unknown, normal MRI	Seizure focus	100% MT	0.5Hz	900s	16 (2 trains/session, biweekly, for 4 weeks)	Clinical seizures decreased during rTMS, and decreased further on follow-up	None reported
Misawa et al 2005	31	Cortical dysplasia	Seizure focus	90% MT	0.5Hz	200s	1	Clinical seizures stopped, resumed in 2 months, and stopped again with rTMS	None reported
Morales et al 2005	8	Neuronal ceroid lipofuscinosis (probable)	Seizure focus	100% MO	6Hz then 1Hz	6Hz: 5s 1Hz: 600s	3 (1Hz, one preceded by four trains at 6Hz)	No change	None reported
Morales et al 2005	16	Perinatal stroke	Seizure focus	76% MO	6Hz, then 1Hz	6Hz: 5s 1Hz: 900s	2 (1Hz, one preceded by 4 trains at 6Hz)	No change	Mild headache and leg pain
Rotenberg et al 2008	14	Rasmussen's encephalitis	Seizure focus	100% MT	1Hz	30mins	9 at 1/day	Total ictal time was significantly reduced during stimulation, but the daily baseline seizure rate remained unchanged.	None reported
Liu et al 2013	46	Unknown, intractable epilepsy since childhood	Right centrotemporal region	70% MO	1Hz	20mins	1	22/day to 8/day	None reported
Liu et al 2013	51	Unknown	Left sensorimotor cortex	100% MT	1Hz	30mins	1	9 prolonged seizures in the 72h prior to administration (20-50 minutes each) to 1 prolonged focal motor seizure (45mins) occurring approximately 48h after rTMS administration. However, 72h after rTMS, his seizures increased in frequency.	None reported

The literature search revealed no reports that used rTMS with video telemetry as an initial therapy for EPC before chronic intracranial stimulation. This technique is non-invasive and has been shown to not interact with other medical equipment commonly used in intensive care settings (Liu et al 2013). It can directly influence cortical excitability before surgical intervention, making it a useful tool both as a stand-alone therapy and alongside a battery of measures for medication resistant EPC.

Though the patient's response varied between some jerks to none in the five years of follow-up the long-term effectiveness of his cortical stimulation treatment was shown when his battery failed increasing his right sided jerking for two weeks and reducing after battery replacement. Therefore, even two years after initial implantation the patient had the potential to develop this EPC, and this was inhibited by the

cortical stimulation. Some side effects were noted, namely uncomfortable sensation in the legs, but these resolved in follow-up after adjusting stimulation parameters. The ability to vary parameters, like dosages of medication suggests an important role for long-term follow-up of patients with cortical stimulators for EPC to optimise their treatment. This is particularly important in responding to changes in the patient's pathology or the position of the stimulating electrodes. This might have explained the recurrence of EPC after his head trauma, though he had returned to his post-cortical stimulation baseline when reviewed six months after trauma. A PubMed literature search for cortical stimulation in EPC revealed three papers (Rizzi et al 2015) (Valentín et al 2015) (Changa et al 2019). Rizzi et al (2015) describe one patient with EPC who had deep brain stimulation in the left caudal zona incerta and significantly decreased their seizure frequency but after two years they required resective surgery of the left motor cortex for the seizures to be completely controlled. Valentín et al (2015) describs two patients where chronic cortical stimulators resulted in an >90% reduction in seizures and abolition of the EPC at 22-month review. Changa et al (2019) reported two patients with EPC who reported an 100% decrease and 99% decrease in seizure frequency at 156 months and 54 months followup respectively. None of these studies reported side effects from the cortical stimulation. There is currently not enough data and too much inter-patient variability to draw strong conclusions about cortical stimulation in EPC, but in the patient reported in this essay and literature search, there is utility to neuromodulation induced by rTMS and cortical stimulation in EPC.

Reported in	Age	Aetiology	Cortical Stimulation Location	Outcome	Adverse events
Rizzi et al 2015	30	Rasmussen encephalitis	Left caudal zona incerta	significantly decreased their seizure frequency for less than 2 years	None reported
Valentín et al 2015	21	Unknown, first seizure was an afebrile tonic–clonic occurring at the age of 7 years	under the dura over the mid posterior aspect of the right frontal lobe	>90% reduction in seizures and abolition of the EPC at 22-month review	None reported
Valentín et al 2015	20	Possible hypoxia due to reported cyanosis following vacuum-assisted delivery	under the dura over the posterior aspect of the left lateral frontal cortex	>90% reduction in seizures and abolition of the EPC at 22-month review	None reported
Changa et al 2019	21	Head trauma	Epileptic foci, left frontal	100% decrease in seizure frequency at 156 months	None reported
Changa et al 2019	25	Encephalitis	Epileptic foci, right temporal	99% decrease in seizure frequency at 54 months	None reported (but allergic reaction to the cable. Removed the DBS 4 years later)

In conclusion we report a case of a patient with EPC whose responsiveness to treatment with rTMS suggested a role for chronic cortical stimulation therapy. This significantly reduced his symptoms although there was some variation in this reduction over the five years of follow-up.

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