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Potential predictive value of repetitive transcranial magnetic stimulation before chronic cortical stimulation for epilepsia partialis continua

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1. Introduction

Epilepsia Partialis Continua (EPC) is classified as focal motor status epilepticus [1]. EPC consists of clonic jerks affecting a part of the body, sometimes aggravated by action or sensory stimuli, occurring for a minimum of 1 h [2]. In this case report, repetitive Transcranial Magnetic Stimulation coupled with EEG (rTMS-EEG) was used to demonstrate that focal cortical stimulation can reduce EPC symptoms and that rTMS-EEG can suggest whether a patient could potentially benefit from long-term intracranial cortical stimulation.

2. Methods

We present a 58 year-old man with EPC consisting on debilitating right arm jerks. He had his first generalised tonic-clonic seizure aged 19, carbamazepine was prescribed, and he was seizure-free until age 42. Subsequently, he developed seizures consisiting on right shoulder jerks that could be induced by arm touch or movement, occasionally involving the right arm and leg, leading to falls. The frequency of seizures progressively worsened, becoming almost continuous during day-time, raising the diagnosis of EPC (video of seizures and EEG in supplementary material). At age 50, an episode of status epilepticus was associated with hypoxic brain injury and aspiration pneumonia, requiring ITU admission. A 3T brain MRI showed left nodular sub-ependymal grey matter heterotopia adjacent to the trigone of the left lateral ventricle (Supplementary Material Fig. 1). Although treatment with carbamazepine (600 mg BD), topiramate (400 mg BD) and phenobarbital (60 mg OD) decreased the number of jerks, they remained frequent enough to reduce right arm function. Inpatient video-telemetry and brain positron emission tomography (PET) were performed for presurgical evaluation. PET showed hypometabolism in the left parietal region.

3. Results

On video-telemetry, isolated jerks of the right arm were associated with left central and parietal epileptiform discharges (Fig. 1A). rTMS (Magstim Rapid) with a figure-of-eight coil was tried as a diagnostic procedure. Two trials of 750 pulses with intensity 1.2 times motor threshold (TMS Motor Threshold Assessment Tool - MTAT 2.0) [3], were delivered at 0.5Hz to the left central fronto-parietal region and were associated with a discontinuation of EPC (supplementary video). An improvement with less severe focal motor seizures was noted for two weeks after the rTMS-EEG session. Intracranial telemetry (iEEG) was planned to assess potential resection or chronic cortical stimulation. A 20-contact subdural grid, two subdural 8-contact strips and one 8-contact depth electrode were implanted over the left posterior frontal and parietal regions. The back-averaging of more than 1500 jerks showed that the leading epileptiform activity was over the central region (Fig. 1B–C, Supplementary Material Fig. 2). A 120-h period of subacute cortical stimulation (0.5–1 mA, 130 Hz, 450 microseconds pulse duration) [4] at different contacts over parietal cortex caused a clear reduction in the frequency of the epileptiform activity and decreased the number of seizures. As the epileptogenic area was located over primary sensory cortex, resective surgery was declined and chronic cortical stimulation (CCS) was chosen for treatment. In the same surgical procedure, iEEG electrodes were removed and a Medtronic Activa™ RC was implanted with two permanent four-electrode stimulating strips over the anterior parietal cortex (Fig. 1D). CCS was activated two days after implantation (1.5 mA, 450 microseconds, 130Hz), and an immediate improvement was noted as the patient was able to move his right arm and hand without inducing clonic jerks. Within five years of follow-up the patient reported occasional recurrence of right arm jerks which mitigated by adjusting stimulation intensity up to 3.5mA. Only a minor reduction on topiramate (300 mg BD) has been tried since implantation.

The efficacy of CCS was anecdotally reassured when CCS battery failed, causing an increase in right sided jerking for two weeks, which reduced after battery replacement.

4. Discussion

rTMS is a non-invasive technique shown to be safe for depression and other psychiatric disorders [5]. There is some risk for seizure induction, particularly with high frequency rTMS. The acute effects of low frequency rTMS-EEG for termination [6] or generation of EDs has been described as potential markers for

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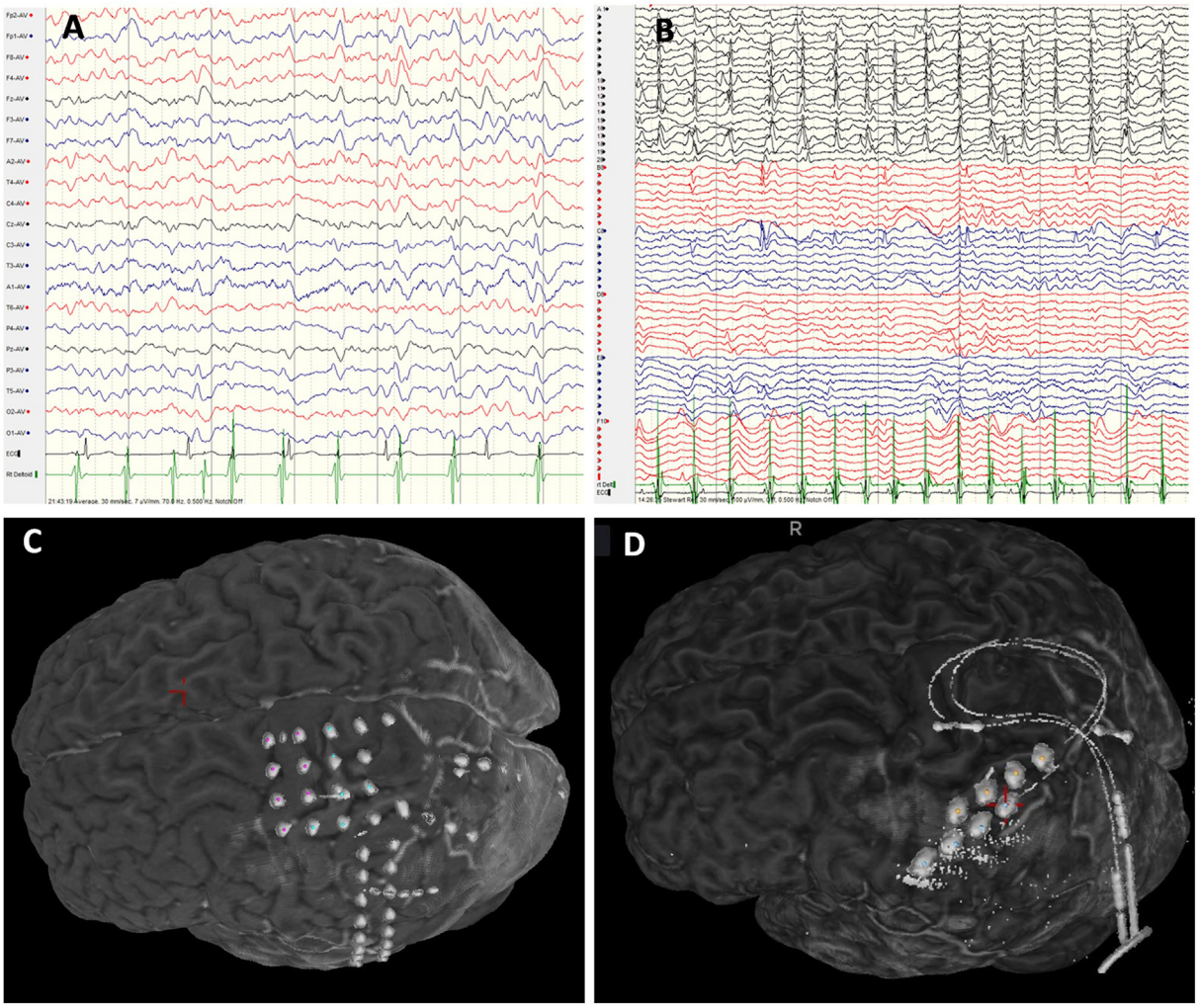

Fig. 1. A) Pre-surgical video telemetry sample showing jerks during sleep associated with very low voltage left centro-parietal spikes (C3; P3). B) Subacute cortical stimulation over the parietal cortex caused a clear reduction in the frequency of the epileptiform activity on EEG. C) Intracranial telemetry subdural electrode grids over the left posterior frontal and parietal region. Red dots indicate contacts located in precentral gyrus (1, 2, 6, 7, 11, 12 and 16) and at postcentral gyrus. D) Post-surgical MRI 3D reconstruction showing electrodes positioned over the left parieto-frontal cortices.

responsiveness to neuromodulatory treatment [7]. rTMS-EEG during video-telemetry helped in deciding this patient's treatment by inducing significant electroclinical improvement, suggesting that CCS could be considered as long-term treatment.

A PubMed literature search revealed seven papers reporting 16 patients with EPC who had rTMS-EEG without significant side effects (Supplementary Material: Table 1) [8]. Thirteen patients showed a reduction in their clinical seizures while three had no change. Given the small number of reported cases, this may not be representative of the number of negative results due to positive reporting bias.

A PubMed literature search for CCS in EPC found three papers (Supplementary Material: Table 2). Rizzi et al. described one patient with EPC with stimulation at the left caudal zona incerta, which significantly decreased seizure frequency but after two years resective surgery of the left motor cortex was required [9]. Valentin et al. described two patients where CCS resulted in >90% reduction in seizures and abolition of the EPC at 22-month review [4]. Chang et al. reported two patients with EPC with 100% and 99% decrease in seizure frequency at 4.5 and 13 years follow-up [10]. No significant side effects were reported from CCS. The ability to modify parameters, and the area of stimulation, suggests that the efficacy of CCS can be improved, and adverse events minimised, in long-term follow-up by appropriate handling.

The pathophysiology of EPC is still unclear, although it has been hypothesised that EPC can originate from an impairment of inhibitory intra-cortical networks activated by thalamo-cortical projections [11]. It is described that the cortex above areas of subependymal heterotopias might also be epileptogenic and this might be related to excellent outcome [12]. In our case, CCS over anterior parietal cortex was chosen as treatment based on intracranial recordings and initial rTMS results.

5. Conclusion

rTMS can modulate ongoing seizures by interrupting neural activity or changing cortical excitability. In our case, the patient's responsiveness to rTMS-EEG suggested a diagnostic predictive role of this technique to estimate CCS efficacy in EPC. Although rTMS-EEG could potentially be useful as stand-alone therapy, the

results reported in the literature are inconsistent and further studies are needed.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property sociated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the corresponding author and which has been configured to accept email from Antonio.valentin@kcl.ac.uk.

Declaration of competing interest

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.01.836.

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