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Clinical letter

Anticonvulsive effect of anterior thalamic deep brain stimulation in super-refractory status epilepticus crucially depends on active stimulation zone—A single case observation

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1. Introduction

Super-refractory status epilepticus has a high mortality, and its treatment remains a challenge for clinical epileptologists. Deep brain stimulation (DBS) is successfully used in pharmacotherapy-resistant epilepsy and larger studies showed significant seizure reduction by high frequency stimulation in the anterior nucleus of the thalamus (ANT) [1]. Furthermore, several case reports indicate that DBS is also effective in the management of status epilepticus. In a recent, very comprehensive publication, Lehtimäki et al. reported resolution of a super-refractory non-convulsive status epilepticus with continuous high-frequency stimulation of the centromedian thalamic nucleus [2]. Other groups found beneficial effects in the centromedian thalamus and recently also in the ANT in generalized or focal status epilepticus [3]. These cases emphasize the feasibility to interact with and eventually disrupt ongoing cortical epileptic activity by DBS.

Here we report a case of a patient with multiple episodes of non-convulsive status epilepticus who was sucessfully treated with bilateral ANT-DBS.

2. Case description

2.1. Previous history

A 66-year-old female patient was admitted to our epilepsy center due to refractory non-convulsive status epilepticus. Eleven months prior, the patient had suffered a series of first-ever bilateral tonic-clonic epileptic seizures. Despite initiation of anticonvulsive treatment with levetiracetam (3000 mg/d), oxcarbazepin (1200 mg/d) and phenytoin (300 mg/d), the patient presented with serial tonic-clonic seizures followed by non-convulsive status epilepticus five and ten months later. She developed progressive deterioration of cognitive function with severe mnestic deficits, apraxia, and episodes of prolonged confusional states. Medication was changed to levetiracetam (4000 mg/d), valproic acid (2500 mg/d) and lacosamide (400 mg/d). After a third episode of prolonged non-convulsive status epilepticus refractory to i.v. midazolam (1 mg/h), the patient was admitted to our clinic.

2.2. Initial assessments

Upon admission, neuropsychological assessment revealed severe deficits including expressive aphasia, apraxia, agraphia, visuo-constructive and mnestic deficits. EEG confirmed the diagnosis of non-convulsive status epilepticus with bilateral temporal to parietal epileptiform discharges (Fig. 1A). Initial treatment included add-on perampanel (8 mg/d), brivaracetam (200 mg/d), phenytoin (300 mg/d) and midazolam (10 mg/h), without effect on either EEG discharges or cognitive function. MRI revealed bilateral cortical and sub-cortical encephalopathy as a possible structural epileptogenic correlate. Extended diagnostics including lumbar puncture, antibody panel for autoimmune

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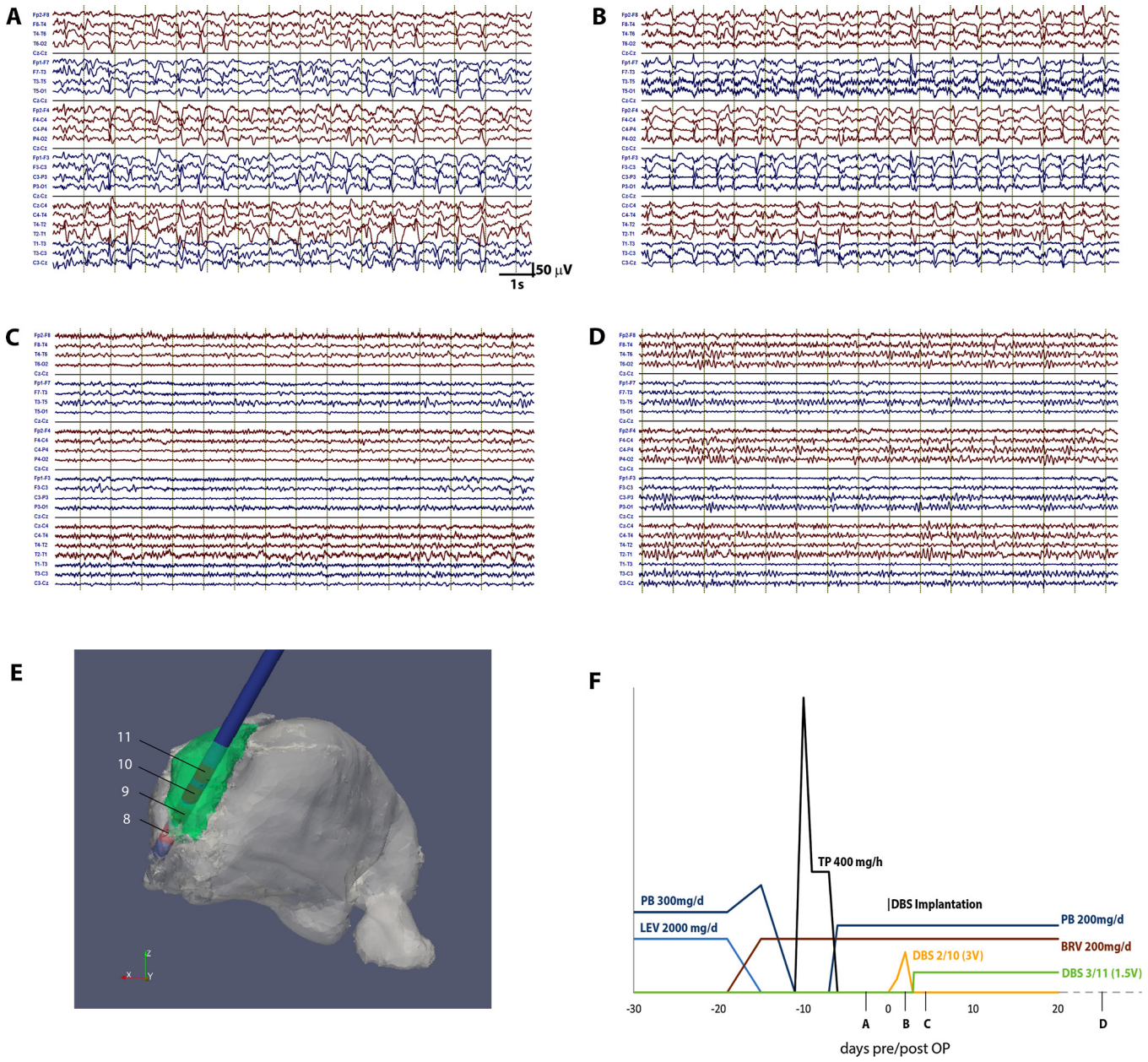

Fig. 1. Synopsis of EEG examinations, DBS electrode implantation and pharmacotherapy. Serial representative EEG epochs are shown at different time points (A) after deep thiopental coma 2 d prior to DBS implantation, (B) on the first post-operative day stimulating on contacts (DBS ON contacts 2 and 10), (C) after changing the active stimulation to more cranial contacts (DBS ON contacts 3 and 11) and (D) 6 months post-operative (DBS ON contacts 3 and 11). E: Lead location based on post-operative CT scan shows upper DBS electrode contacts in the anterior thalamus bilaterally (three dimensional model reconstruction of the left electrode). Stereotactical coordinates: contact 0 (left side): x = 3.34 lat, y = 1.54 post, z = 5.72 sup; contact 8 (right side): x = 3.96 lat, 1.28 post, 6.93 sup. Coordinates of active contacts 3/11: left: x = 5.33 lat, 1.12 ant, 10.72 sup; right 5.44 lat, 2.42 ant, 13.87 sup; ACPC at 27.49 mm. Panel F represents a summary of pharmacotherapy, DBS implantation and changes in DBS parameters in the peri-operative phase. PB: phenobarbital, LEV: levetiracetam, TP: natrium thiopental, BRV: brivaracetam. Letters on the time axis refer to the time points of EEG examinations (A–D).

encephalitis, FDG-PET scan, angiography and brain biopsy did not reveal any signs of systemic or neurodegenerative underlying disease. We initiated deep burst suppression anesthesia with thiopental (1–2 burst/min) for 72 h. However, non-convulsive status epilepticus persisted also after gradual phase-out of thiopental.

2.3. Operative intervention

Based on the temporal to parietal predominance of the epileptiform discharges, we decided to offer ANT-DBS as an individual salvage therapy. Target selection was based on the hypothesis that modulation of the Papez' circuit directly influences the active epileptic network in our patient by an efferent inhibitory effect. DBS leads (Medtronic Model 3383) were implanted bilaterally in the ANT based on direct MRI targeting. Lead positions were verified by post-operative CT (Fig. 1E). DBS was initiated intraoperatively in the caudal part of the ANT (contacts 2 and 10, 145 Hz, 90 µs, continuous mode, 1 V). Anticonvulsive medication remained unchanged during and after implantation (Fig. 1F).

2.4. Post-operative outcome

On the first post-operative day, the EEG showed persistent status epilepticus and stimulation amplitude was therefore increased to 3 V (145 Hz, contacts 2 and 10). We then observed worsening of epileptic

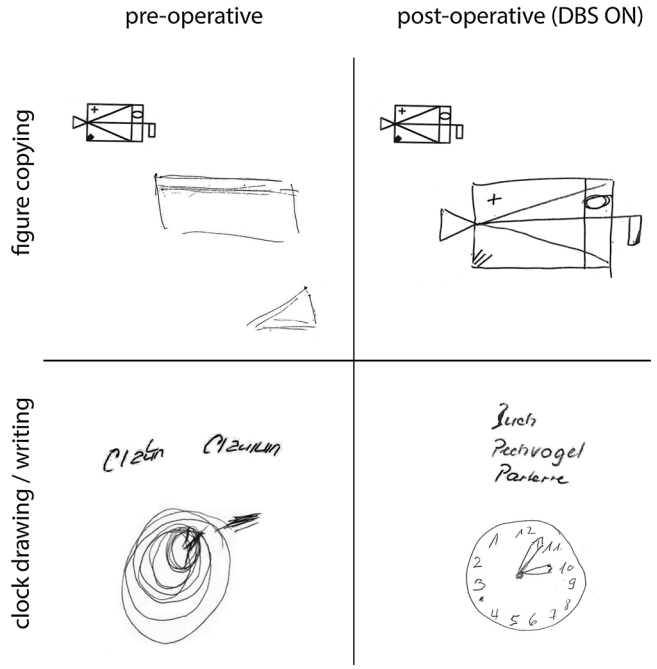

Fig. 2. Illustration of pre- and post-operative neuropsychological performance. In the pre-operative assessment during ongoing status epilepticus, the patients showed severe visuo-constructive deficits in geometric figure copying (upper left). Clock drawing from memory illustrated severe constructional apraxia with impressive motor perseveration (lower left). In the attempt to write the name 'Claudia' the patient showed severe alteration of writing with deteriorated orthographic production and impaired character reproduction as a correlate for apraxic agraphia, representing the disruption of movement plans of skilled writing (lower left). During the follow-up assessment 3 months post-operatively (right panels), the patient showed full recovery of constructional apraxia and writing skills (normal writing of German words 'Buch', 'Pechvogel', 'Parterre'). The improvement to normal writing skills was linked to full suppression of parietal epileptiform discharges, supporting the role of the parietal cortex for apraxic agraphia. The clock face was drawn mirror-inverted, indicating mild residual visuo-spatial impairment.

activity and the patient suffered from two bilateral tonic-clonic seizures within the next 24 h. Thus, we changed the stimulation contacts to the most dorsal part of the ANT (contacts 3 and 11). The patient showed an immediate positive clinical response with improvement of vigilance and reduction of epileptiform discharges in the EEG. Twenty-four hours later, the EEG was free from epileptiform potentials (Fig. 1C) and the patient showed a dramatic improvement of cognitive function, most prominently in mnestic and visuo-spatial domains. Repeat EEGs remained free from epileptic discharges and the patient was sent to neurological rehabilitation 10 days after implantation.

2.5. Long-term and neuropsychological outcome

We performed standardized clinical and neuropsychological follow-up assessment 3 months post-operatively. The patient reported further substantial recovery of her cognitive function. The formal neuropsychological assessment showed only slight persistent episodic memory deficits for verbal information and mild slowing of information processing speed. Interference control and working memory capacity were just below age-adjusted average (Fig. 2). In follow-up EEG examinations, we observed a normalization to alpha background activity (6 months post-OP, Fig. 1D). The patient remained seizure-free for all seizure types (currently 18 months post-implantation).

3. Discussion

We here report a case illustrating successful immediate and long-term resolution of super-refractory status epilepticus after high frequency stimulation in the dorsal part of the ANT. This case corroborates the feasibility to terminate ongoing generalized epileptic activity by DBS and adds further insights to the treatment of status epilepticus. The core finding of this case was that the efficacy of DBS crucially depends on the exact lead location and minor changes of the stimulation site show immense impact on the clinical response.

In recent years, a paradigm shift has taken place in epilepsy research towards an understanding of epilepsy as a network disease. DBS offers an elegant approach to influence this pathological epileptic network based on the hypothesis that electrical stimulation at well-defined nodal points may induce a state transition from an epileptic towards a non-epileptic state. This network-level effect of DBS might explain the intriguing finding that high frequency stimulation of deep brain nuclei reduces seizures originating from spatially distant cortical neuronal ensembles. Our case corroborates this hypothesis considering the striking effect on stimulation response at different locations within the anatomical target: whereas the antero-medial part projects to the orbito-frontal and anterior cingulate cortex, the antero–ventral thalamic nucleus shows higher connectivity towards the retro-splenial cortex and the parietal neocortex [4]. Now, along the implantation trajectory in our patient (Fig. 1E) the upper (more cranial) lead contacts lie closer to the antero-ventral nucleus. We therefore conclude that the anticonvulsive effect may be based on a pinpoint interaction with the epileptogenic network including the antero-ventral thalamus connected to the parietal neocortex.

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.

Declaration of Competing Interest

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

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