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Low frequency centromedian thalamic nuclei deep brain stimulation for the treatment of super refractory status epilepticus: A case report and a review of the literature

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Super refractory status epilepticus (srSE) refers to a SE that fails to respond to 1st and 2nd line treatments and persists after 24 hours of anaesthesia carrying increased risk of mortality, morbidity, and disability. Centromedian Thalamic Nucleus DBS (CMN DBS) appears to provide some benefit in refractory generalised epilepsy [1,2], but its efficacy and the best stimulation parameters for this condition remain unclear. We report the case of a 15-year-old right-handed girl with normal development and no family history of epilepsy. Bilateral tonic-clonic seizures (BTCS) started at the age of 5 leading to srSE with Paediatric Intensive Care Unit (PICU) admission and thiopentone coma induction. The possibility of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (MAS) was raised and she was discharged 4 weeks later on levetiracetam, steroids and cyclosporine with cognitive, language and behavioural difficulties.

She developed brief asymmetric tonic seizures with occasional clusters of 20–30 seizures/day. Multiple AEDs (phenytoin, levetiracetam, carbamazepine, lacosamide, lamotrigine, perampanel, zonisamide, stiripentol) and ketogenic diet provided limited benefit. A second srSE occurred aged 9 with a 6-week PICU admission and further regression in cognition. Following discharge, she had significant sleep issues and clusters of daytime focal seizures and unresponsiveness. Brain MRI was normal. An extensive presurgical work-up with scalp telemetry, PET scan and ictal-SPECT suggested multiple potential epileptogenic regions and excluded suitability for epilepsy surgery leading to VNS implantation.

A 3rd srSE occurred aged 14, with uncontrolled, up to 30 brief seizures/hour, requiring further admission to PICU. Thiopentone and several other drugs (felbamate, stiripentol, IVIG, steroids, anakinra, and cannabinoids) were unhelpful. Most seizures started with left head-eye deviation and flickering for 1 minute, followed by arm stiffening. She also had focal tonic seizures with clonic elements and BTCS. Respiratory depression caused by infections and high drug doses complicated her condition.

Repeat scalp telemetry showed focal ictal onset over the left/midline parietal region, followed by right anterior quadrant build-up of ictal activity. After 80 days in the PICU she was transferred to King's College Hospital (KCH) for CMN DBS implantation in an attempt to terminate the srSE. The New Clinical Procedure Committee approved the technique, and the family provided informed consent.

DBS (Medtronic 3389 electrodes- (Fig. 1A,B) was activated on the implantation date with bipolar stimulation contact 1 negative, contact 2 positive, 130Hz, 90 μs, 1.5 mA. After initial minor improvement in seizure frequency, seizure control worsened and DBS parameters were changed to bipolar simulation contacts 0, 1, 2 negatives, contact 3 positive, 60Hz, 90 μs, 3V. Electrode impedance was checked with each parameter adjustment. A 12-h pause of DBS caused clinical deterioration leading from focal to bilateral tonic-clonic seizures (Fig. 1C). The DBS was re-started with the same stimulation parameters and an increa se of stimulation intensity to 5V.

As focal seizures remained almost continuous, 48 hours later the DBS parameters were changed to bipolar stimulation contact 1 negative, contact 2 positive, 6Hz, 300 μs, 3V. No clear stimulation artefacts or recruitment rhythm was noted at the scalp EEG at any stimulation parameter (Fig. 1E).

After 4 days, the seizure frequency decreased significantly and she was more alert, enjoying uninterrupted seizure-free sleep periods. She was discharged from HDU to the paediatric ward on the 17th day. Seizures remained focal over left parietal and midline region without spreading anteriorly. On the 22nd day, a deterioration in sleep pattern was noted, and the stimulation parameters were set to 60Hz/90 μs during the night and 6Hz/300 μs during daytime, without sleep improvement and with re-emergence of 5–6 focal seizures/hour (Fig. 1C)

Based on prominent focal EEG activity after DBS implantation, a review of brain MRI and PET suggested an area of possible focal cortical dysplasia over the left parietal region. Stereo-EEG (SEEG) exploration was agreed and DBS was switched off on the 27th day, before the implantation of depth electrodes. Detailed description of the SEEG implantation strategy is out of the scope of this letter but SEEG recorded clinical and electrographic seizures with onset over the left temporoparietal region. Resection of the area led to more than 90% reduction in clinical seizures and the patient was discharged home with a rehabilitation plan. Neuropathology showed possible, but non-conclusive, cortical dysplasia.

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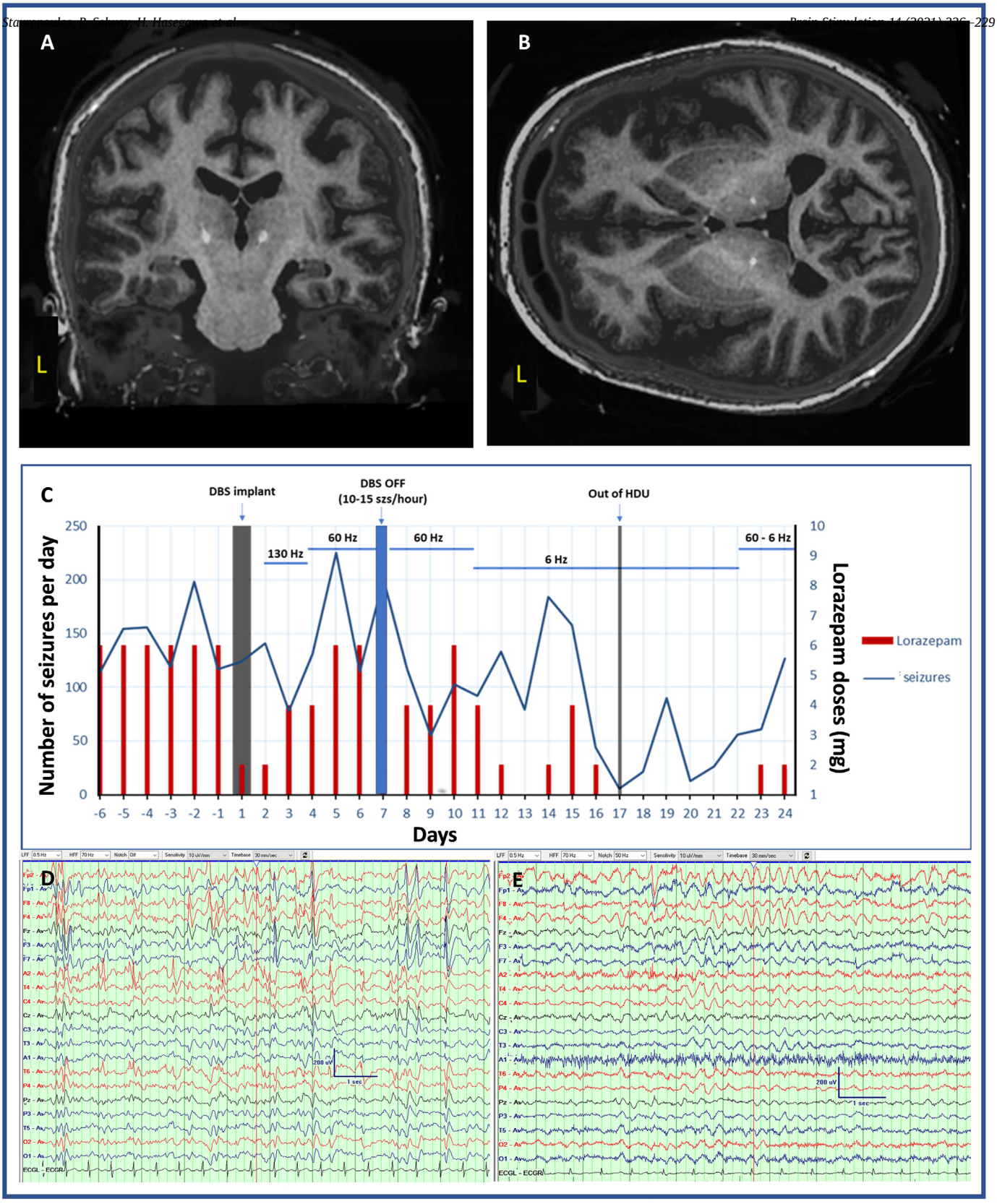

Fig. 1. (A) Axial view of pre-implantation MRI fused with post-implantation CT; (B) coronal view of pre-implantation MRI fused with post-implantation CT showing the final position of the DBS electrodes. Note that the left DBS electrode is slightly lateral to the target, but within stimulation distance of the CMN; (C) Retrospective count of seizures by IS and DJ who were blind to treatment. Seizures were summation for every 24 hours. The different DBS stimulation parameters and the lorazepam injection for severe clinical seizures are marked through the graph. At the time of DBS implantation her medication was Melatonin, Brivaracetam, Clonazepam, Sodium Valproate and Cannabidiol. No changes in medication were done during the whole period of DBS stimulation apart from PRN lorazepam doses given for prolonged or frequent tonic clonic seizures; (D) Typical EEG recording before DBS implantation; (E) EEG recording during DBS stimulation at 6 Hz (day 16).

Discussion

DBS can be considered as a potential "rescue" treatment for patients with super-refractory status epilepticus. Seven cases have been reported describing the efficacy of DBS for srSE (Table 1-supplementary material). The timing of DBS implantation after srSE onset is variable (28–59 days) and the ideal DBS target for srSE has not been established. In three cases, the DBS was implanted at the anterior nucleus of the thalamus for absence srSE [3], convulsive srSE [4] and non-convulsive rSE[5]. In four cases, the CMN was targeted either due to common variable immunodeficiency-associated encephalomyelitis [6], possible encephalitis (autoimmune/infectious) complicated with cardiac arrest [7], or febrile infection-related epilepsy syndrome (FIRES) [8]. In a previous case implanted at KCH [7] and in one of the two FIRES cases at another institution [8], the srSE terminated with a vegetative state probably due to hypoxic-ischaemic brain injury in the 1st case, and prolonged status in the 2nd case. Based on these outcomes, earlier DBS implantation could be considered to reduce time in srSE and avoid permanent neurological injury.

There is a lack of consensus regarding the best DBS parameters. High-frequency stimulation (130Hz [4,8], 145Hz [3,5], or 180Hz [6], with a 70–90 μs pulse width) appeared to be effective in the treatment of generalised seizures, successfully resolving the srSE (Table 1). Occasionally, the improvement in frequency of generalised seizures evolves to frequent focal or multifocal seizures. In order to reduce the severity and burden of focal seizures, low-frequency stimulation (6Hz, 300 μs) have been tried in three previously reported cases [7,8]. In our patient, this parameter appeared to reduce focal/multifocal seizures after a stimulation period of 5–10 days (Graph 1). Other variations in DBS parameters such as monopolar/bipolar, current/voltage or continuous/discontinuous stimulation have not been properly studied in these cases.

One potential hypothesis for the apparent benefit of CMN low-frequency stimulation is that CMN thalamic nuclei are functionally connected with the fronto-parietal structures of the cortex [9] and this could cause highly-synchronized brain activity, facilitating inhibitory mechanisms which could be involved in the termination of focal seizures during srSE [10]. Continuous low-frequency stimulation of these nuclei may disrupt seizure generation in connected cortical epileptogenic regions, reducing number and/or severity of focal seizures.

In summary, srSE is a life-threatening condition with a complicated standard treatment and CMN-DBS could be considered a "rescue" therapeutic option. High-frequency stimulation appears effective in controlling generalised seizures and may be considered as a clinical option for substantially reducing intensive care time, limiting the potential side effects of srSE medication, and preventing further neurological damage. Low-frequency CMN DBS stimulation could provide an additional clinical benefit reducing the severity and frequency of focal/multifocal seizures.

Author contributions

AV, EH, RS and HH designed the DBS implantation and the stimulation parameters. IS, CR and DJJ reviewed and analysed the seizures' data. IS and AV wrote the manuscript and prepared the seizure graph. All authors reviewed and approved the final version of the manuscript.

Competing/conflicting interests

AV has received honorarium for lectures and consultancy from Medtronic Ltd. The rest of authors declare that they have no competing interests.

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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.2020.12.013.

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