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Case study

Centromedian thalamic nuclei deep brain stimulation and Anakinra treatment for FIRES – Two different outcomes

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ABSTRACT

Febrile infection-related epilepsy syndrome (FIRES) is a severe epilepsy disorder that affects previously healthy children. It carries high likelihood of unfavourable outcome and putative aetiology relates to an auto-inflammatory process. Standard antiepileptic drug therapies including intravenous anaesthetic agents are largely ineffective in controlling status epilepticus in FIRES. Deep brain stimulation of the centromedian thalamic nuclei (CMN-DBS) has been previously used in refractory status epilepticus in only a few cases. The use of Anakinra (a recombinant version of the human interleukin-1 receptor antagonist) has been reported in one case with FIRES with good outcome. Here we describe two male paediatric patients with FIRES unresponsive to multiple anti-epileptic drugs, first-line immune modulation, ketogenic diet and cannabidiol. They both received Anakinra and underwent CMN-DBS. The primary aim for CMN-DBS therapy was to reduce generalized seizures. CMN-DBS abolished generalized seizures in both cases and Anakinra had a

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positive effect in one. This patient had a favourable outcome whereas the other did not. These are the first reported cases of FIRES where CMN-DBS has been used.

1. Introduction

Febrile infection-related epilepsy syndrome (FIRES) is a devastating epileptic disorder that affects children aged over 2 years, presenting with explosive onset of super-refractory status epilepticus following a nonspecific febrile illness. It is a rare condition with an estimated incidence of 1/1000000[1] and the aetiology is unknown, although immunological factors have been postulated.[2] FIRES has a biphasic presentation, with an acute phase of seizure activity lasting 1–12 weeks, followed by a chronic phase, characterized by refractory seizures. The outcome is usually poor with a mortality of up to 30%, refractory epilepsy in 90–100% and varying degree of intellectual disability present in virtually all cases.[3] FIRES is characteristically unresponsive to antiepileptic drugs and immunotherapy.[1] A consensus definition for FIRES has been recently published.[4]

Therapies such as ketogenic diet and cannabidiol have been reported to be beneficial, with reduction of seizures in the acute phase and an improved motor and cognitive outcome in the chronic phase.[5–7]

Here we report two paediatric patients with FIRES in whom two novel treatments, deep brain stimulation targeting centromedian thalamic nuclei (CMN-DBS), and Anakinra, were used.

2. Case 1

A previously well 9-year-old boy presented with focal seizures with evolution to bilateral tonic-clonic convulsions, following a four-day history of fever, vomiting and headaches. Seizures were characterized by facial twitching evolving to ipsilateral arm and leg jerking with tonic upwards eye deviation and impairment of awareness. There was frequent secondary generalization. Despite escalation of anti-epileptic treatment the seizure frequency increased and the patient was started on thiopentone infusion on day 8 (D8). Burst-suppression pattern on EEG was achieved for a total of 4 days. He received extensive anti-epileptic drug treatment but continued to have almost continuous seizures. At this stage he was managed maintaining supratherapeutic levels of phenobarnitone (70–100 mg/L, therapeutic range 10–40 mg/L), ketogenic diet, cannabidiol and midazolam (up to 10 mcg/kg/min) and ketamine (up to 45mcg/kg/min) IV infusions (Fig. 1A; Supportive material: Table 1).

Infectious, inflammatory, metabolic and genetic investigations were completed. Brain MRI showed basal ganglia, external capsule and cortex signal abnormalities (Supportive material: Table 1 and Fig. 2-A,B).

On D27 CMN-DBS was implanted and stimulation commenced at 4 mA, frequency 130 Hz and pulse width 90 mcs. The primary goal of this therapy was to reduce the generalised seizures probably provoked by evolution of focal seizures to bilateral tonic-clonic, stabilise vital function and transfer the patient out of intensive care. There was a significant response to neuromodulation with additional reduction in seizures and focal seizures no longer demonstrated evolution to bilateral hemispheric involvement (Fig. 1A). Nevertheless, he continued to have frequent focal seizures mostly arising independently from bilateral fronto-central regions. With the aim of reducing the number and/or severity of the focal seizures, the neuromodulation settings were changed to 2 mA/6 Hz/450 mcs and this change was associated with a transient reduction of focal seizures. During the following 4 days no additional phenobarbitone doses to manage episodes of seizure escalation were required. To determine the contribution of CMN-DBS to seizure control stimulation was switched off on D39 for 72 h and this resulted in an increase of focal seizures with evolution to bilateral convulsive seizures and increased requirement of additional phenobarbitone doses. Once CMN-DBS was restarted there was a reduction in both clinical and electrographic seizure activity. Anakinra was commenced on D43 in order to improve seizure control further so that the patient could be discharged from the intensive care setting (titrated up to 5 mg/kg/day over 14 days). From D51 seizures decreased in frequency and on D60 these stopped. He was transferred out of intensive care unit on D74. The last 24 h EEG on D85 showed one single focal seizure.

The patient was seizure-free for three weeks but seizures then re-emerged with once weekly short episodes of facial twitching. Over this post-acute period the patient had behavioural difficulties with frequent anger outbursts and aggression. CMN-DBS was switched off 8 months after implantation and this was not followed by clinical deterioration or increase in seizure frequency. Fifteen months after presentation, he was still on Anakinra and was having short focal seizures with an average of 2–5 seizures per month. After an intensive period of rehabilitation, he had good motor function, no significant cognitive impairment and was attending mainstream school. Behavioural difficulties also improved.

3. Case 2

A previously well 5-year-old boy presented with generalized tonic-clonic seizures following a four-day history of fever, abdominal pain and coryza. The seizures continued despite aggressive treatment and thiopentone infusion was started on D3. Burst-suppression pattern on EEG was achieved for 3 days. Multiple antiepileptic and immunomodulation treatments

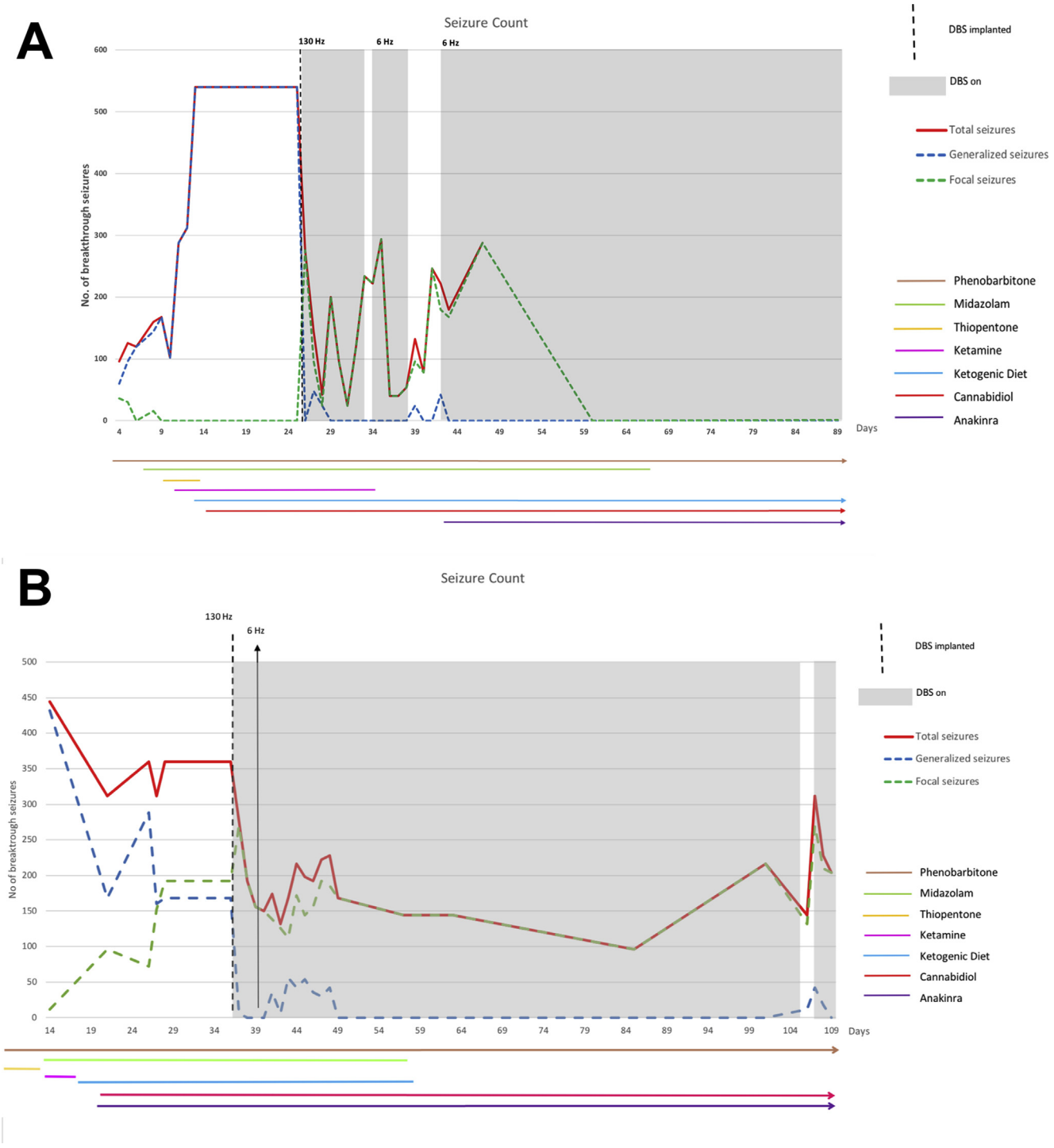

Fig. 1 – A retrospective count was made of breakthrough seizures (clinical and subclinical) by RS who was blind to treatment. Seizures were counted at four 1 h time points (0800, 1400, 2000, 0200) and multiplied by 6, to give 24 h estimate of number of breakthrough seizures. Awake and sleep time periods were captured each day. A: Patient 1 - DBS stimulation was started on day 27 and there was an immediate but nonsustained decrease of total seizures and almost abolishment of secondary generalization. This was confirmed with the reappearance of generalized seizures after DBS switch off on day 39. B: Patient 2 - DBS stimulation was started on day 37 and there was immediate marked reduction in total of generalized seizures with several days when no generalized seizures were counted. There was also a reduction of focal seizures but this effect was not sustained. C: Intra-operative CT and pre-operative MRI co-registration images of Patient 2 showing contact placement within the centromedian thalamic nuclei. CMN-DBS implantation technique: bilateral CMN electrodes were placed with assistance of a stereotactic neurosurgical robot (Neuromate, Renishaw). Trajectory planning was performed using preoperative 3T-MRI volumetric t1-sequences (Siemens, Magnetom Prisma). Electrode trajectory was defined on planning software (Neuroinspire, Renishaw) from a point on the skull just anterior to the coronal suture and 2 cm lateral to

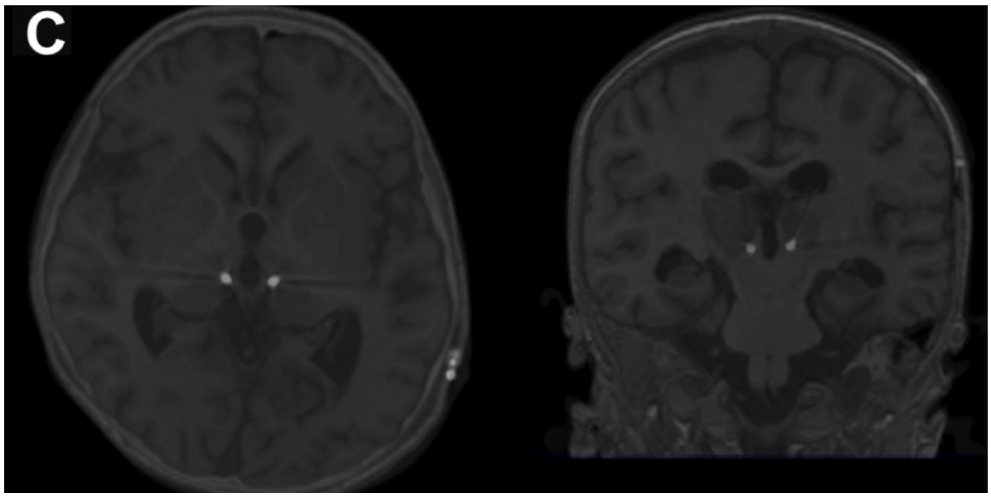

Fig. 1 – (*continued*)

were initiated (Fig. 1B; Supportive material: Table 1). While on thiopentone treatment he became hypotensive and required inotropic support but he never had a prolonged hypoxic/hypotensive event. He was transferred to our centre two weeks after presentation when he was still having frequent seizures characterized by alternating facial twitching, lip smacking and limb twitching/tonic contraction. Supratherapeutic levels of phenobarnitone (80–150 mg/L, therapeutic range 10–40 mg/L) were maintained. Extensive infective, inflammatory and metabolic investigations were completed and showed negative results. Brain MRI at D12 showed severe diffusion restriction in keeping with excitotoxic oedema (Supportive material: Table 1 and Fig. 2-D).

Anakinra was started on D22 and titrated up to 10 mg/kg/day. In view of ongoing frequent seizure activity, CMN-DBS was implanted and bilateral neuromodulation commenced on day 37 at 2 mA/130 Hz/90 mcs (Fig. 1C). Immediately after the DBS implantation a stop in the generalised seizures was observed for 4 days (Fig. 1B). As he continued to have frequent focal seizures mostly arising independently from bilateral fronto-central regions, the neuromodulation settings were changed to 2 mA/6 Hz/450 mcs and this change was associated to a reduction of focal seizures, and a transient increase of generalised seizures.

Again to determine the effect of CMN-DBS stimulation was switched off on D105 for 24 h and a reappearance of generalized seizures was observed.

Following tracheostomy he was weaned off ventilation but remained in a vegetative state with frequent focal seizures. The patient was discharged from the intensive care unit on D62. Anakinra was discontinued after a total of three months of treatment. Eighteen months after presentation there was no improvement in his state of consciousness or seizure activity.

4. Discussion

We report two cases of FIRES treated with CMN-DBS and Anakinra with different outcomes.

Patient-1 had a good response to CMN-DBS and discharged out of intensive care after Anakinra was started. He was left with refractory epilepsy with infrequent self-limited short focal seizures and is attending mainstream school.

Conversely, Patient-2 was started on Anakinra first and CMN-DBS was implanted 15 days later. Although there was a reduction in the total number of seizures he continued to have very frequent focal seizures and remained in vegetative state.

DBS is an emerging treatment for patients with refractory epilepsy.[8] The best results for DBS targeting CMN have been noted in generalized seizures and cessation of generalized epileptiform discharges and it is less effective in focal seizures.[9,10] Only three cases of DBS used to treat super-refractory status epilepticus have been reported so far and none in FIRES. Valentin et al. reported that CMN-DBS was effective in resolution of generalized seizures in a 27-year-old with several episodes of cardiac arrest and refractory status epilepticus.[11] Lehtimäki et al. reported a case of an 17-year-old boy with common variable immunodeficiency-associated encephalomyelitis and super-refractory status epilepticus who was successfully treated following CMN-DBS.[12] Both our cases showed a clear response to DBS treatment with cessation of generalized seizures. A re-emergence of generalized seizures was seen in both patients when stimulation was

the midline, towards a point 10 mm lateral to the posterior commissure. Robotic registration was carried out using a Leksell frame with intra-operative CT. Electrodes (Medtronic lead-3389) were implanted and connected to a subcutaneously placed pulse generator (Medtronic Activa). Initial parameters for potential inhibitory stimulation: bipolar stimulation contacts 1–2+, frequency of 130 Hz, pulse width of 90 μs and intensity of up to 5 mA. Second stimulation parameter with excitatory component: bipolar stimulation at contacts 1–2+, frequency of 6 Hz, pulse width 450 μs and intensity of up to 2 mA.

temporarily switched off. This suggests a neuromodulation effect of CMN-DBS.

It has been postulated that the pathogenesis of FIRES involves systemic inflammation and the release of pro-inflammatory cytokines and activation of innate immune mechanisms in seizure-prone brain areas.[2] Furthermore, It has been shown that pro-inflammatory cytokine interleukin-1 beta (IL-1β) is involved in the mechanisms of epileptogenesis, febrile seizures[13] and FIRES[14] and its blockade can be used for seizure control.[15] Anakinra is a recombinant version of the human IL-1R1 antagonist and inhibits the action of IL-1β. It has been recently used for the treatment of generalized pharmacoresistant epilepsy[16] and FIRES,[17] in paediatric patients with signs of systemic inflammation, namely increased cerebrospinal fluid IL-8 concentrations. There is theoretical and clinical evidence that in autoimmune disorders early aggressive immunomodulatory treatment leads to better outcomes.[18]

Intrathecal production of inflammatory cytokines was not tested in our patients. Patient-1 had raised CSF neopterins which is an indirect marker of inflammation and Anakinra initiation resulted in sustained reduction of seizures (Fig. 1A). Patient-2 did not respond to Anakinra. It is possible that the different response to IL-1R1 blockade seen in our two patients was a result of different pathogenic mechanisms.[14] Analysis of proinflammatory cytokines in CSF pre and post Anakinra treatment may help in better understanding of the pathophysiology in FIRES.

Although there was no clear response to any other antiepileptic drugs, cannabidiol, ketogenic diet, or other immunomodulation therapies, it is possible that synergistic effects of different treatment modalities may have played a role in Patient-1's clinical response.

Additionally, in a retrospective observational setting it is challenging to distinguish natural history of the disease from the effect of therapeutic intervention. Nevertheless, in the published literature all patients that have had such prolonged intensive care stay and significant seizure burden combined with similar extensive brain MRI changes had invariably poor outcome.[19]

In summary, FIRES is still an ill-defined severe epileptic syndrome with probable multiple aetiologies and pathogenic mechanisms. An immune mediated process has been proposed but the upregulation of pro-inflammatory cytokines can also be secondary to seizure activity. Genetic factors responsible for patients' susceptibility for super-refractory status are yet to be identified and this could explain the variable responses to both interventions. Further studies are needed to better understand this disorder and efficacy of different treatments. Nonetheless, CMN-DBS and Anakinra should be considered as treatment options for patients with refractory status epilepticus in FIRES. CMN-DBS can be a valid option for acute symptomatic treatment when generalized seizures are a prominent feature. Anakinra targets directly the proposed autoinflammatory aetiology of FIRES and the favourable outcomes reported in our patient and a previous case[17] indicate that it should be considered as a treatment option.

Disclosure of conflict of interests

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.08.001.

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