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Responsive Neurostimulation Therapy for Super-Refractory Autoimmune Epilepsy

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Background: Immunotherapy remains the cornerstone for treatment of autoimmune epilepsy; however, some remain super-refractory despite immunotherapy and anti-seizure medications (ASMs).

Methods: Case-series study of two patients with super-refractory AE treated with bilateral hippocampal responsive neurostimulation (RNS).

Results: Case 1: A 37 year-old woman presented with frequent (5-8/day) focal seizures with flushing and disabling chest pain of 4 years. Seizures are refractory to intravenous methylprednisolone and immunoglobulin and 9 ASMs. Serum autoimmune epilepsy panel was positive for Glutamic acid decarboxylase 65 (GAD65) antibody (250mg/dL). Brain MRI showed left mesial temporal sclerosis (MTS) and fluorodeoxyglucose positron emission tomography (fdg-PET) showed bitemporal hypometabolism. Evaluation for occult malignancy was negative. Bilateral independent temporal seizures were recorded. She was treated with RNS utilizing bi-hippocampal electrodes. Right hippocampal onset seizures were aborted within 8 weeks, however left hippocampal onset seizures were only reduced by 25%. At 18 months, she continued to experience seizures, albeit at reduced frequency.

Case 2: A 39 year-old woman presented with frequent focal and bilateral tonic clonic seizures. CSF was inflammatory but neuroimmunology panel was negative. Seizures are refractory to intravenous methylprednisolone and immunoglobulin, plasma exchange, Rituximab, Cyclophosphamide, and Azathioprine, 11 ASMs, and vagus nerve stimulation therapy. Brain MRI showed bilateral MTS. Screening for occult was unrevealing. Bilateral independent temporal seizures were recorded, and she was implanted with bi-hippocampal RNS electrodes. Within 8 weeks, seizure frequency was reduced by over 50%. Further, the RNS data disclosed catamenial clustering and led to the initiation of progesterone. At 6 months follow-up, she reported significant seizure reduction.

Conclusions: RNS has a role in the treatment of super-refractory autoimmune epilepsy. RNS helps track seizure burden objectively and may inform anti-seizure medication optimization in this patient population.

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Updated Data on the Tocilizumab Treatment in New Onset Refractory Status Epilepticus

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Background: New onset refractory status epilepticus (NORSE) is defined by new onset status epilepticus (SE), showing no response to at least 2 anti-epileptic drugs (AEDs) without evidence of other structural, toxic, or metabolic causes in patients who have been otherwise previously healthy. As no clear etiology has been established for NORSE, autoimmune or paraneoplastic causes account for the majority of NORSE cases with an identifiable cause. Even though immunotherapies including steroid, immunoglobulin, and rituximab have been tried to treat NORSE, approximately 60% of the patients had poor functional outcomes, suggesting need of the next line of immunotherapy. With updated data on the tocilizumab treatment in NORSE patients, we investigated the therapeutic potential of the tocilizumab, interleukin-6 receptor inhibitor, as new candidate of immunotherapy for NORSE.

Methods: In this study, updated data on two additional NORSE patients were analyzed to the previous data published. In a prospective cohort for autoimmune encephalitis since June 1, 2012, of which patients who have been admitted to Seoul National University, the patients who were diagnosed with NORSE with poor response to conventional immune therapy including steroid, immunoglobulin, and rituximab and treated with tocilizumab from August 2015 to November 2018 were subjected to further analysis.

Results: Compared to the previous data of 7 SE patients, 7 out of 9 SE patients showed cessation of SE with a median interval of 5 days from the initiation of treatment. According to our data, patients who responded to tocilizumab tended to show either clinical or electrophysiological improvement at most within the second cycle of treatment, which means early response to treatment. Two patients experienced infection as adverse event after tocilizumab treatment, and one patient on updated data showed no response to tocilizumab even after two cycles of treatment.

Conclusions: Tocilizumab treatment resulted in cessation of SE in 7 out of 9 patients according to our results. Therapeutic effects of tocilizumab on SE patients who do not show definite response to conventional immunotherapy are to be further studied with alternative immunologic pathway, and further prospective study with larger number of patients is warranted.

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Combination therapy of immunoglobulin, Rituximab, and Tocilizumab in treating acute autoimmune encephalitis

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Background: A considerable portion of autoimmune encephalitis (AE) does not respond to conventional immunotherapies and subsequently have poor outcomes. Tocilizumab, an anti-interleukin-6 antibody, has some effect on treating AE refractory to first-line immunotherapies and Rituximab. We aimed to determine the efficacy of the combination therapy of immunoglobulin (\pm steroid), Rituximab, and Tocilizumab (IsRT) in treating acute AE over conventional treatment options.

Methods: This institutional cohort included seventy-nine consecutive patients with antibody-proven AE. Acute treatment regimens were categorized as IsRT, IsR, and Is. Patients' clinical severity was assessed at every two weeks for the first three months, at every month for the next

three months, and then at every three months, using the Clinical Assessment Scales in Autoimmune Encephalitis (CASE, 9 clinical items, score range 0–27). Outcomes were categorized into excellent (CASE scores 0–4), moderate (CASE scores 5–19), and poor (CASE scores 20–27) at the last follow-up. The 3-month clinical responsiveness to immunotherapies was designated as the early outcome parameter and defined as the major improvement of CASE scores (≥ 4) within the first 3 months.

Result: As acute treatment regimens, 33 patients received IsRT, 32 received IsR, and 14 received Is. Compared to the conventional treatment groups (IsR and Is), IsRT group exhibited higher initial CASE scores, higher level of CSF leukocyte, and more frequent use of ventilator care. 3-months clinical responsiveness was the single most powerful parameter associated with excellent or poor final clinical outcomes. Multivariate analysis showed that along with the initial CASE score, IsRT regimen was associated with higher frequency of achieving clinical responsiveness at 3 months. Frequency of serious adverse effects were comparable among the treatment regimens.

Conclusion: Combination treatment of immunoglobulin, Rituximab, and Tocilizumab in the acute phase of AE might enhance the clinical responsiveness to immunotherapy and therefore be a good treatment strategy.

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Electrographic Predictors of Successful Weaning from IV Anesthetics in Refractory Status Epilepticus^{*}

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Background: Intravenous third-line anesthetic agents (IV-TLA) are titrated in refractory status epilepticus (RSE) to achieve either seizure suppression or burst suppression on EEG. However, little data exist to help guide clinicians in the weaning of IV-TLA in RSE. This study sought to evaluate several quantitative measures of EEG activity during IV-TLA weaning in RSE, employing novel analytic techniques to help identify patients that may successfully wean from IV-TLA.

Methods: We identified patients diagnosed with RSE who underwent at least one IV-TLA wean, excluding patients presenting with cardiac arrest. A successful IV-TLA wean was defined as the discontinuation of an IV-TLA without the development of recurrent status epilepticus for at least 48 hours. A wean failure was defined as either recurrent status epilepticus or the resumption of IV-TLA (other than for patient comfort). Two quantitative analyses were performed: a frequency-based analysis in which the power of spectral components of the EEG signal were calculated, and a novel spatial-correlation-based analysis, in which EEG data were used to generate continuous maps of functional connectivity during each IV-TLA wean. The power and ratios of spectral components and the parameters characterizing functional network topology were then used to compare successful and unsuccessful weans. The results of these quantitative analyses were used to train a classifier to predict wean outcome.

Results: Twenty-six patients undergoing 40 anesthetic weans (18 successes, 22 failures) were identified. Quantification of signal power in discrete frequency bands revealed no significant differences between successful and unsuccessful weans. Analysis of functional connectivity measures revealed that successful IV-TLA weans were characterized by larger, more highly-clustered spatial networks of activity. Specifically, functional networks from patients undergoing successful IV-TLA weans had a significantly higher mean density, higher mean clustering coefficient, fewer independent components, and larger largest components than those from patients that failed anesthetic wean.

Conclusions: Distinct patterns of changes in the spatial networks of functional connectivity emerge during successful anesthetic weans that are absent in wean failures. Identifying EEG features that dynamically emerge during successful IV-TLA weaning may help optimize anesthetic management for RSE by preventing an unnecessary excess of wean attempts or weaning duration.

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The Proposed Multimodal Mechanism of Action of Cannabidiol (CBD) in Epilepsy: Modulation of Intracellular Calcium and Adenosine-mediated Signalling

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Background: Although commonly misrepresented, cannabidiol (CBD) does not act directly through cannabinoid receptors at physiologically achievable concentrations. CBD has shown anticonvulsant properties in non-clinical studies and antiseizure effects in clinical trials of Dravet and Lennox-Gastaut syndromes with a unique multimodal molecular target profile, distinct from other antiepileptic drugs. We present preclinical evidence summarising CBD's leading mechanisms of action in epilepsy.

Methods: Preclinical evidence suggests CBD reduces neuronal hyperexcitability through multiple mechanisms, including modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55), extracellular calcium influx via transient receptor potential vanilloid type 1 (TRPV1) channels and adenosine-mediated signalling.

Results: CBD antagonises GPR55 at excitatory synapses. The inhibition of intracellular calcium release decreases excitatory currents and seizure activity. GPR55-mediated modulation of neurotransmission was potentiated in excitatory neurons and reduced in inhibitory neurons in a chronic epilepsy model. CBD potently blocked the GPR55-mediated increase of miniature excitatory postsynaptic current frequency in pyramidal neurons in both healthy and epileptic tissue. CBD did not affect the GPR55-mediated increase of excitatory neurotransmission in inhibitory neurons in healthy tissue. CBD's anticonvulsant properties were attenuated in GPR55 knockout (KO) animals.

CBD desensitises TRPV1 channels. The resultant decrease in extracellular calcium influx decreases neurotransmission. The dose-dependent CBD-mediated increase in seizure threshold