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Targeted Electroconvulsive Therapy for Super Refractory Status Epilepticus: A Case Report and Literature Review

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Introduction

Electroconvulsive therapy (ECT) has been shown to be effective for a number of medical conditions that manifest in a general hospital, including malignant catatonia, neuroleptic malignant syndrome, toxic delirium, and status epilepticus. Although over 20 case reports suggest that ECT may be effective in cases of medically intractable status epilepticus, it is a rarely used treatment. We present a case of a patient with drug-resistant epilepsy partialis continua persisting for 51 days before ECT was successfully implemented and discuss the theory and practice of ECT for status epilepticus.

Case Report

Mr. J, a 51-year-old man with severe alcohol use disorder, presented to the emergency department (ED) in January 2015 with new-onset status epilepticus, first manifesting with generalized tonic-clonic seizures, then progressing to right-sided focal motor seizures of the upper extremity and face. Computed tomography (CT) scan demonstrated a new anterior-inferior left temporal lobe hemorrhagic parenchymal contusion, presumably due to repeated falls. After 8 days, resolution of epileptiform activity on electroencephalogram (EEG) was achieved after the administration of lacosamide, levetiracetam, phenytoin, and midazolam. On the day of discharge, Mr. J's EEG continued to show mild-to-moderate diffuse slowing in the left hemisphere. He was discharged on hospital day 14 on levetiracetam 1000 mg bid, phenytoin 300 mg bid, and lacosamide 100 mg bid.

Mr. J then presented to the ED in early March of 2015 after being found down with right upper extremity and right side facial twitching after reportedly missing his anticonvulsants that day. On initial examination, Mr. J was noted to be awake but mute, with diminished muscle strength in the right-sided extremities and continued right-side facial twitching. Laboratory values revealed no underlying cause, and magnetic resonance imaging (MRI) showed only the previous left hemorrhagic temporal lobe contusion. He was administered lorazepam 5 mg and phenytoin 800 mg but the seizures persisted. He was transferred to the Neuroscience ICU where he was loaded with phenytoin 1100 mg, lacosamide 400 mg, and levetiracetam 4000 mg over the next 24 hours.

Mr. J continued with seizure over the next several days, leading to intubation and administration of midazolam, lorazepam, valproic acid, and topiramate. Despite trials of multiple first- and second-line agents, the EEG continued to demonstrate focal motor status emanating from the left hemisphere, with additional epileptogenic cerebral dysfunction arising from the left frontal regions of the hemisphere. By hospital day (HD) 10, Mr. J was placed in a pentobarbital coma for burst suppression. For the next month, status epilepticus persisted, despite trials of ketamine (13,586 mg daily), felbamate (2800 mg daily), zonisamide (200 mg daily), methyprednisolone (1000 mg daily), carbamazepine (1800 mg daily), perampanel (12 mg daily), and an experimental neurosteroid medication, allopregnanolone. Brain positron emission tomography (PET) showed evolving hypermetabolic ictal focus over the left lateral and middle temporal lobes, areas essential to speech and motor function, rendering Mr. J a nonsurgical candidate. By HD 50, at the suggestion of the neurology team, his family agreed to a trial of ECT for seizure control. Both the psychiatry and neurology teams participated in the consenting process.

From days 52–54, the patient received a total of 9 bitemporal and 2 bifrontoparietal ECT treatments (Table 1A). The Thymatron System IV machine was used for all treatments, utilizing 900 mA current amplitude, 1.0 ms pulse width, pulse frequency 70 Hz, train duration 8 seconds, total charge 504 millicoulombs. Maximum device output (100% energy) was employed given previous literature and the number of anticonvulsants *in vivo* at the time of stimulation. Prior to each treatment series, oral and intravenous anticonvulsants were held, flumazenil was used to reverse benzodiazepine effects, glycopyrrolate was given to avoid prolonged asystole from repeated nonconvulsive stimulations, and a nondepolarizing neuromuscular blocking agent was used to prevent stimulation-induced muscle contractions and hyperkalemia (rocuronium and vecuronium). Video EEG monitoring was temporarily discontinued during each session, to avoid potential damage to the EEG amplifiers from the ECT. Motor seizure activity was monitored using the cuff method on the left leg.

Only 1 out of 6 stimulations produced a detectable seizure on HD 52. Therefore, Mr. J was weaned off of pentobarbital during the subsequent ECT treatments, with midazolam utilized for burst suppression. On HD 53, 2 out of 3 stimulations produced seizures of 47 and 12 seconds' duration. On HD 54, a bifrontoparietal electrode montage was utilized, based on the hypothesis that application of the stimulus closer to the frontal motor strip seizure focus might lead to increased anticonvulsant effect in that area. Two out of 2 stimulations produced robust seizures of 87 and 89 seconds, presumably owing to the taper of pentobarbital (Table 1B).

Following the eleventh ECT treatment, Mr. J had a distinct change on continuous EEG monitoring, from diffuse beta waves intermixed with alpha waves from benzodiazepine effects, to paroxysmal theta activity with maximum electronegative focus over the left anterior and middle temporal lobe. At first there was concern that ECT had worsened the seizure activity, prompting cessation of the treatments. However, 3 days post-ECT treatment, the background EEG pattern improved, and the patient had spontaneous eye opening. Clobazam was then initiated. One week following ECT, Mr. J exhibited eye tracking, and after the second week, he was responding to commands. Seventeen days after ECT treatment, he had no seizure activity on EEG. On HD 96, Mr. J was discharged to a long-term rehabilitation facility. At the time of discharge, he was able to verbalize short phrases. More than 1 year later, he demonstrated no further episodes of status epilepticus and progressed to verbalizing full sentences. He remains on his discharge medication regimen: lacosamide 300 mg bid, levetiracetam 3000 mg bid, clobazam 20 mg bid, phenytoin 225 mg tid, and carbamazepine 600 mg tid.

Discussion

One of the indications for ECT, as specified by the American Psychiatric Association, is intractable seizures.¹ A recent systematic review of 19 cases of ECT in status epilepticus found that 57% reported improvement, but the level of evidence supporting ECT for status is generally poor.² Two subsequent case reports documented successful use of ECT for status epilepticus in a 16-year-old cerebral palsy patient and a 4-year-old patient with FIRES (febrile infection-related epilepsy syndrome).^{3,4} We acknowledge that in this literature, it is difficult to ascertain whether cessation of status after ECT is a result of the ECT itself, due to spontaneous recovery, or due to simultaneous therapies. Rarely is status broken immediately following electroconvulsive stimulation. However, we believe our case is a clear example of how ECT contributed to cessation of status when extensive medical therapy alone failed. The temporal relationship between the changes of EEG seizure characteristics suggests that the ECT treatments were integral in the evolution of the status and the patient's response to medication. This case was also unique for its individualized electrode placement targeting the seizure focus to increase efficacy, a technique that is gaining ground as both invasive and noninvasive forms of brain stimulation move toward tailored delivery of electromagnetic energy to functional brain abnormalities.⁵

Theory of Anticonvulsant Effect of ECT

Although the exact mechanism of ECT is unknown, several known consequences of ECT suggest how it may be beneficial in seizure disorders. First, it is well established that seizures occur as a result of abnormal excessive or synchronous neuronal activity in the brain.⁶ The possible anticonvulsant effects of ECT may be due to direct or indirect neurotransmitter alterations that diminish aberrant neuronal activity. Glutamate is transiently increased after a motor and EEG seizure, followed by an increase in gamma-aminobutyric acid (GABA), leading to overall increased cortical inhibition.⁷ Evidence suggests that cortical GABA concentration can increase twofold following a single course of ECT.⁸ Furthermore, ECT not only produces increases in GABA but also resets the ratio of inhibitory to excitatory stimulus.⁹ This might provide an explanation as to why the patient's

EEG transiently worsened following ECT but eventually progressed to resolution of the status.

Second, while convulsions are known to be an important component of the ECT effect, there is ample evidence showing that electrode placement and parameters of electrical stimulation modulate both efficacy and side effects. In our case, it is reasonable to wonder if the placement of electrodes over the area of seizure focus facilitated beneficial changes preferentially in that region. Mr. J's SE was assumed to be a result of his chronic subdural hematoma, which resulted in an area of hypermetabolic potential epileptogenic focus. Although the ECT stimulus itself was clearly excitatory (causing seizure), its metabolic and vascular postictal effects induced at or near the epileptogenic zone may have reduced neuronal excitability and firing. There is an initial ictal increase in cerebral blood flow and metabolism in ECT, followed by longer-term decreases in blood flow after multiple treatments, all of which may have contributed to neuronal stabilization.¹⁰ Furthermore, his EEG changed significantly after the last 2 treatments employing the targeted montage, progressing to paroxysmal theta waves in the left temporal region, a possible reflection of regional functional change. This theory is supported by effects seen with transcranial magnetic stimulation (TMS) delivered to seizure foci in intractable epilepsy, in which seizure pauses and lasting seizure reductions have been observed directly after TMS pulses.⁵

Third, trophic downstream consequences of ECT include bilateral increases in regional cortical thickness, increases in glial cells, and increases in inhibitory GABAergic interneurons.¹¹ However, it is not clear how these physiologic changes might contribute to the anticonvulsant effect.

Practical Application of ECT for Status Epilepticus

When providing ECT for status epilepticus, consultant psychiatrists should be mindful of the following modifications to typical ECT procedures: (1) The neurology team should be involved in the consenting procedure, and ideally should sign the consent form with the ECT provider, as the ECT is being done for a neurological rather than psychiatric indication. (2) Discontinuation of unhelpful anticonvulsants and temporary cessation of all anticonvulsant medications before the procedure will help make ECT-induced seizures more robust. (3) Precautions to prevent over-saturation or damage to video or continuous EEG amplifiers during ECT should be taken. (4) Reversal agents such as flumazenil can be helpful if benzodiazepines are part of the treatment regimen or are used for burst suppression. (5) Glycopyrrolate is recommended given the theoretical risk of asystole when ECT is performed at maximum energy in status patients. (6) Use of a nondepolarizing (vs depolarizing, i.e., succinylcholine) paralysis agent is recommended to avoid compounding the risk of hyperkalemia in bed bound patients susceptible to rhabdomyolysis. (7) There does not appear to be a benefit to minimizing the amount of charge delivered—maximum FDA-approved machine output should be used. (8) Multiple treatments in the same day are typical in these cases.

Conclusion

Consultant psychiatrists will be increasingly called upon to recommend or apply noninvasive brain stimulation techniques in the general hospital. In the case of ECT for status epilepticus, more research is needed to fully comprehend the nature of its anticonvulsant effects.

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TABLE 1A.

ECT Treatment Details

ECT treatment number	Hospital day	Lead placement	Energy administered	Medications administered (mg)	Length of motor seizure (seconds)	Length of EEG seizure (seconds)
1	52	Bitemporal	100%	Rocuronium 50	No seizure	No seizure
				Flumazenil 0.2		
				Glycopyrolate 0.1		
2	52	Bitemporal	100%		No seizure	No seizure
3	52	Bitemporal	100%		No seizure	No seizure
4	52	Bitemporal	100%	Flumazenil 0.9	8	10
5	52	Bitemporal	100%		No seizure	No seizure
6	52	Bitemporal	100%		No seizure	No seizure
7	53	Bitemporal	100%	Rocuronium 100	47	47
				Flumazenil 1		
				Glycopyrolate 0.4		
8	53	Bitemporal	100%		12	12
9	53	Bitemporal	100%	Flumazenil 1	14	14
10	54	Bifrontoparietal	100%	Vecuronium 10	87	89
				Flumazenil 1		
				Glycopyrolate 0.4		
11	54	Bifrontoparietal	100%		89	89

TABLE 1B.
Maximum Daily Dosage of Medication Used During and After ECT Hospital Day

	ECT	Lacosamide	Leviteracetam	Carbamazepine	Pentobarbital	Midazolam	Fosphenytoin	Clobazam	Phenytoin
52	Yes	100	6000	1800	2664	864	975		
53	Yes	800	6000	1800	2664	665	675		
54	Yes	600	6000	1800		240	600		
55		600	6000	1800		288	600		
56		600	6000	1800		288	600		
57		600	6000	1800		288	600		
58		600	6000	1800		48	600		
59		600	6000	1800		192	675		
60		600	6000	1800		192	675	30	
61		600	6000	1800		32	675	40	
62-88		600	6000	1800			675	40	
89-96		600	6000	1800				40	600