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Editorial

Deep Brain Stimulation in Intractable Epilepsy: Proposed Advancements and Future Hope

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Epilepsy is one of the oldest and commonest neurological diseases and presently considered a common global problem. The prevalence of epilepsy is estimated to be one in hundred in the general population with a distinctly higher degree of affliction in underdeveloped and developing countries. This is further compounded by more than one-third of all epilepsy cases not responding satisfactorily to optimal pharmacotherapy and constituting intractable epilepsy (IE). Management of IE poses a challenge to neuro-clinicians even today and comprises of adjunctive alternative therapies like ketogenic diet, epilepsy brain surgery, vagal nerve and deep brain stimulations.

Deep brain stimulation (DBS) is establishing as a highly effective therapy for several types of movement disorders with its application steadily expanding to encompass several selected neurological and psychiatric disorders refractory to conventional management. In 1997, the Food and Drug Administration (FDA) first approved thalamic DBS for tremor. Irving Cooper, considered as a pioneer of brain stimulation in patients with epilepsy, observed relief in seizures upon cerebellar stimulation in 1972; in 1980, Cooper with Upton also performed thalamic stimulation in patients with epilepsy (PWE) paving the way for discovery of more anatomic targets. Resultantly, in present times, DBS is emerging as a first line alternative therapy in selected PWE that are unsuitable candidates for epilepsy brain surgery and/or VNS.

Rapid eye movement sleep (REMS) is known to offer natural dual influence (anti-epileptogenic and antiepileptic) in PWE. Stimulation of acetylcholine neurons (AChN) in the pedunculopontine nucleus (PPN) is known to induce REMS leading to suggestion of a specific and strong role of lesions of AChN in epileptogenesis by some researchers. On therapeutic grounds, adrenocorticotrophic hormone is hypothesized to decrease spasms in West syndrome not only through corticosteroids but also through a direct action on the pontine tegmentum, probably via REMS; the anticonvulsant, lamotrigine, has also been found to block α4β2nAChRsmediated currents. It has also been demonstrated that the PPN is strongly affected by the functional reorganization of neurocircuitry associated with kindling and the pedunculopontine neurons are involved in network changes in the kindling model of temporal lobe epilepsy, a common form of IE.

Jaseja has advocated PPN stimulation (PPNS) as an effective means of providing strong antiepileptic environment and enhancement of natural protection against epileptogenesis and occurrence of epileptic seizures by enhancing REM sleep.

Despite establishment of DBS as an effective adjunctive therapeutic strategy in patients with IE, the efficacy and success of the FDA approved thalamic DBS have been found to be limited to only intractable complex partial seizures raising a strong requirement of exploration and establishment of novel DBS targets with superior efficacy and broader therapeutic spectrum. The PPN stimulation, although a novel technique in IE, possesses several distinct advantages over the thalamic DBS as follows: (a) its neurophysiology is clearly known (b) its mode of action simulates natural antiepileptic influence in humans in the form of REM sleep; hence, also a minimum risk of adverse effects (c) broader therapeutic spectrum as focal as well as generalized seizure activities are suppressed during REM sleep (d) convenient and wider range of programming and (e) demonstration of induced recovery of disrupted physiological activity of the neural pathways involved in sleep homeostasis.

In current thalamic DBS practice, the utility of electroencephalography (EEG) is limited to the verification of placement or location of the DBS electrode in the target thalamic site obtained in the form of a driving response. Selection of DBS parameters (DBSPs) is made conventionally by trial and error and final settings are determined by periodic assessments of the clinical response and seizure profile until an optimal control over the intractable seizures is achieved; this invariably requires multiple sessions and hospital visits with incurrence of significant expenditure by the patients.

Additionally, with the trial and error mode of selection of the DBSPs extended over multiple sessions, the therapeutic efficacy and success of thalamic DBS have been found to be largely limited to only one class of intractable seizures (IS), namely complex partial seizures (CPS); even in the SANTE trial, only CPS were significantly reduced.

It is well documented that EEG-desynchronization is associated with potent antiepileptic influence; moreover, powerful long term anti-kindling effect has also been demonstrated with desynchronizing stimuli with even reversal of the kindling process. In Jaseja's opinion, these effects can sum up to effectively suppress or even arrest the ongoing process of epileptogenesis in addition to exercising powerful control over the intractable seizures. In absence of the exact mechanism of the antiepileptic action of thalamic DBS, it has been proposed that thalamic DBS exerts its antiepileptic influence by chronic reduction of cortical excitability; however, in view of the above mentioned multifactorial antiepileptic effect of EEG-desynchronization, it has been suggested that the focus of DBS therapeutic strategy should preferably be shifted from excitability to induction of a desynchronization state. In his personal experience also, Jaseja has observed that only a correct combination of frequency, pulse-width and voltage of stimulation is able to successfully induce optimal degree of EEG-desynchronization and the detection, maneuverability and successful attainment of which is possible only with a simultaneous EEG monitoring. Fortunately, the EEG response to changes in the DBS settings or adjustments is immediately visible in the simultaneous EEG recording.

Therefore, Jaseja has proposed that EEG-guided approach to the selection of DBSPs in patients with IE is likely to be associated with a significantly higher degree of therapeutic efficacy and success in comparison to that achieved by the conventional trial and error mode. He has also postulated that the degree of therapeutic efficacy and success could conform to the degree of EEG-desynchronization inducible by DBS in a particular patient.

Resultantly, Jaseja outlines several advantages of his proposed EEG-guided therapeutic strategy in the selection of DBS parameters as below:

1. A strictly targeted approach with a distinct objective of inducing EEG-desynchronization and development of a potent antiepileptic state with possibly an additional anti-kindling influence.
2. Minimum sessions (possibly only one), thereby reducing hospital visits and expenditure.
3. Potentially effective and comparatively lower values of DBSPs, therefore, likely to be associated with (a) minimum adverse effects and (b) minimal device battery consumption; thus, prolonging device-battery life.
4. Since, EEG-desynchronization exerts a generalized antiepileptic influence irrespective of the form of seizure disorder, application of Jaseja's proposed EEG-guided strategy in the selection of DBSPs can potentially expand the therapeutic spectrum of thalamic DBS and encompass a wider range of intractable seizures (underpinned with strong pathological neuronal synchronization) that are currently unamenable to the trial and error mode in a manner analogous to higher therapeutic efficacy achieved by intracranial EEG-guided resection of the epileptogenic cortex (zone) in patients with IE undergoing epilepsy brain resective surgery in comparison to the surgery without EEG-guidance.

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