Commentary

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Drug Resistant Epilepsy: Current Challenges and the Path Forward

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Epilepsy is a tendency of brain to have recurrent unprovoked seizures. Traditionally, the diagnosis of epilepsy has been made after having two unprovoked seizures greater than 24 hours apart. According to recent revised definition by International League Against Epilepsy (ILAE), epilepsy definition includes one unprovoked (or reflex) seizure and a probability of further seizures similar to general recurrence risk (at least 60%) [1]. Important and perhaps the most challenging subset of patients with epilepsy is patients who have drug resistant epilepsy. The chance of seizure freedom progressively diminishes with successive antiepileptic drug failures. According to the study by Kwan and Brodie, after failure of first two antiepileptic drugs, the chance of seizure freedom with third or subsequent drug trial is approximately 3%. ILAE defines drug resistant epilepsy as Failure of adequate trials of two well tolerated, appropriately chosen and used antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure freedom [2]. The aim of this article is to provide overview of current management and outline typical work up for drug resistant epilepsy.

The Drug resistant epilepsy (DRE) accounts for approximately one third of patients with epilepsy. DRE carries significant mortality and morbidity risks. According to the study done in childhood epilepsy, cumulative mortality was 37% for those with symptomatic epilepsy and 12% for those with idiopathic/cryptogenic epilepsy [3]. Similar data from the adult epilepsy population suggest that people with epilepsy have 11 times higher odds of dying from the pre-mature cause compared to that of the general population and unaffected siblings [4]. The risk of death from external causes in people with epilepsy who had a lifetime psychiatric diagnosis was 10 times higher than in people with no epilepsy and no psychiatric disorders [4]. Among the causes of death in people with epilepsy, sudden unexpected death in epilepsy (SUDEP) is of particular importance. Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause of death [5]. The risk of SUDEP is highest in the cohort of intractable epilepsy patients (0.5-1 percent a year) [6].

Although challenging, several treatment avenues exists for the treatment of patients with DRE. The management of DRE patients requires multi-disciplinary approach. The first step is to establish the diagnosis. This often requires video-EEG study at epilepsy centre. Once the diagnosis is established, the next step is to rule out pseudo-resistance. Improper drug and dose choices and noncompliance are among the leading factor contributing to pseudo-resistance. Once diagnosis of drug resistant epilepsy is established, next step is to establish surgical candidacy often referred to pre-surgical work up. The goal of pre-surgical work up is localize epileptogenic zone by tailored evaluation. The evaluation usually requires epilepsy protocol MRI, neuropsychological test and PET scan. In selected cases, MEG scan, ictal SPECT and invasive EEG monitoring may be required. In carefully identified surgical patients, epilepsy surgery can offer substantial benefit over the continued medical management. In temporal-lobe epilepsy, the study has established superiority of surgical arm with cumulative proportion of patients who were free of seizures impairing awareness was 58% in the surgical group and 8% in the medical group [7]. The outcome from epilepsy surgery has been showed to be sustained in a long term follow up [8]. In addition to the seizure control, ample data exists to show that successful epilepsy surgery is associated with the improvement in quality of life, higher employment and sustained improvement in anxiety and depression [9,10]. Devices are emerging as a strong and viable treatment option for DRE patients. Currently available devices can be broadly categorized in two categories. First, open loop stimulation devices which deliver stimulation at a pre-determined parameter regardless of seizure onset; this category includes vagal nerve stimulator and deep brain stimulation. Second, closed loop stimulation arm that delivers localized stimulation in response to seizure onset; this category include responsive neurostimulation device [11]. As a rule of thumb, neuromodulation from the devices have improved efficacy over period of time [3]. Overall, these devices serve as an adjunctive treatment and reserved for the patients in whom respective surgery is not appropriate.

Drug resistant epilepsy (DRE) represents unique set of challenges. Despite of the challenges, recent advances in surgeries and devices in the treatment of epilepsy have made it possible to achieve seizure freedom and/or reduction in majority of these patients. Patients with DRE should be

identified and referred early to the comprehensive epilepsy center.

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