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## SPECIAL ISSUE

*“Treatment of Severe Epileptic Syndromes”*

### Editor

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*‘The various aspects of drug resistant epilepsies’*

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## EDITORIAL

# The Various Aspects of Drug Resistant Epilepsies

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Epilepsy is one of the most common neurologic disorders with a prevalence of approximately 6:1000. The periods of highest incidence occur in patients younger than 1 year and in patients older than 75 years. Some of the most difficult-to-control seizure types and epilepsy syndromes occur during childhood and include complex partial, tonic, and atonic seizures, infantile spasms, and the Lennox-Gastaut syndrome [1]. Medical management with antiepileptic drugs (AEDs) remains the first-line treatment in patients with epilepsy [2]. Drug resistance is the main determinant of low quality of life in persons with epilepsy, at least in industrialized countries. The proportion of patients whose epilepsy is drug-resistant varies depending on the definition of the condition, the study methods used, and the characteristics of the population being studied [3].

There are several factors to be considered in a definition of medical intractability, including the number of AED failures, minimum frequency at which seizures must occur to be considered intractable (daily, monthly, and so forth), duration of unresponsiveness to medication, epilepsy syndrome involved, cause of seizures in the absence of a clear-cut epilepsy syndrome, and patient age at the onset of seizures. When 2 AEDs for the correct seizure type and in adequate doses fail, there is only a 5–10% probability of achieving seizure control with a third drug [2]. However, overall it has been estimated that between 30 and 40% of

patients fail to achieve enduring seizure control with available AEDs. New generation AEDs have widened our ability to tailor drug choice, but their benefits relate to improved tolerability rather than greater efficacy. Indeed, probably no more than 5–10% of patients with severe drug-resistant epilepsy achieve freedom from seizures when started on a new AED [3].

There are some factors that have been repeatedly identified as potential predictors of refractory epilepsy. There are several researches to understand the mechanisms of drug-resistance in literature. Franzoni et al. discuss the various predictors identified so far; in this review authors argue as identifying clinical predictors for pharmaco-resistant epilepsy early in the course of the disorder may be important for directing patients to an

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effective non-pharmacologic treatment, such as surgery, ketogenic diet or vagus nerve stimulation.

Ketogenic diet is currently a therapeutic option for the treatment of epilepsy other than anticonvulsant drugs, for which there is a growing interest in Europe and worldwide, mainly due to the persisting number of refractory patients and the adverse side effects of antiepileptic old and new drugs. Coppola et al. provide a comprehensive review of literature data regarding the use of the diet in the different types of epilepsies and epilepsy syndromes, trying to better understand the main evidence-based indications for its use.

Vagus Nerve Stimulation (VNS) is an effective alternative treatment for patients with refractory epilepsy. Nevertheless, information regarding VNS is still limited.

In a non randomized, prospective study Zamponi and collaborators report their clinical safety and effectiveness of VNS in 100 patients with drug resistant epilepsy. Patient's age at implant ranged from 0,64 to 51,04 years (mean age 15.3 years). The mean follow-up time was 54,8 months. Patients suffered from Lennox-Gastaut Syndrome, partial epilepsy with drop attacks and secondary bysynchronism on the EEG (Lennox Gastaut-like) or Partial Epilepsy without drop attacks. Data collection forms were designed for prospectively gathering data on each patient's history, seizures, drug therapy, implant device settings and side effects. Tuberous Sclerosis Complex (TSC) is a multisystem autosomal dominant genetic disorder resulting from mutations in one of two genes, TSC1 and TSC2. Pathologically TSC is characterized by abnormal cellular differentiation and proliferation, as well as abnormal neuronal migration. The majority of patients with TSC have epilepsy, although the mechanisms underlying epileptogenesis

remain unknown. Seizures onset is frequently during the first year of life, and in a sizable proportion of individuals tend to be refractory to antiepileptic drug treatment. Curatolo et al. review the progress in understanding drug resistant seizures in TSC, from molecular pathogenesis to the pathophysiological mechanisms of epileptogenesis, and the rationale for appropriate medical and surgical treatment.

Lennox-Gastaut syndrome is a childhood epileptic encephalopathy characterised by polymorphic seizures and neuropsychological decline. The most characteristic seizures are tonic fits, atypical absences and atonic seizures, in that order. Treatment options for patients with LGS are limited because of the resistance of seizures to pharmacological treatment. Seizure freedom appears to be unrealistic in some refractory epilepsies, especially LGS. Verrotti et al. discuss newer antiepileptic drugs (Felbamate, Lamotrigine, Levetiracetam, Topiramate, Rufinamide, Vigabatrin, Zonisamide) in the treatment of Lennox-Gastaut syndrome. Investigation of the effects of newer medications might help to identify treatments that, when used in the early stages of the disorder, might have long-term beneficial effects on seizures and the associated comorbidities.

The spectrum of neuropsychiatric disorders associated with continuous spike-waves during slow wave sleep (CSWS) syndromes is widely debated. Although seizures and CSWS disappear within puberty, heterogeneous neuropsychological and behavioural disorders can persist. This feature has increased the interest in etiopathogenesis and negative prognostic factors of these conditions. Delayed diagnosis and appropriate therapy, the high frequency, generalization, early onset, prolonged duration and drug resistance of EEG paroxysmal abnormalities are all unfavourable prognostic factors for

neuropsychological and behavioural evolution.

In a case report, Parmeggiani and collaborators describe five patients with drug resistant CSWS presenting different clinical-EEG features. This study underlines the need to be aware that CSWS can develop and that early diagnosis is very important to start an antiepileptic treatment.

Although no medication can cure any of the epilepsies yet, the infant, child, and adolescent have never had a greater number of options for palliative treatment. Because of advances made in the efficacy of AEDs to reduce the seizure burden and in the adverse-effect profiles of those medications, the outcome for each patient can be optimized. The choice of AED is influenced by various factors such as the natural history of the epilepsy (when known), cognitive status of the child, comorbid medical conditions, and medications, making a simple algorithm impossible.

We hope that this supplement could contribute to translate results from clinical research into the daily practice of all physicians involved in epilepsy care, and to eventually improve the health outcome of our patients.

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