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Review Article

Refractory Epilepsy in Children: A Short Review

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Abstract: Epilepsy is one of the serious neurological conditions, and 30 to 40% of people with epilepsy have seizures that are not controlled by primary medication. It is estimated that 10–20 % children with epilepsy, usually have negative effect on the education, social life. Absence of response to 2 anti-epileptic drugs tolerated at reasonable doses is considered refractory for all working purpose. Advances in imaging and electrophysiology have revolutionized the management of children with refractory epilepsy. Several newer antiepileptic drugs with novel mechanism of action and Ketogenic diet along with advanced epileptic surgery and nerve stimulation has changed the lives of the patients along with better outcome.

Keywords: Refractory epilepsy, keto diet, vagal nerve stimulation.

INTRODUCTION

10–20 % children with epilepsy develop drug refractory epilepsy [1]. The incidence of refractory epilepsy remains high despite many new antiepileptic drugs (AEDs). According to Task Force of the ILAE, it is defined as "Failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". This requires application of the intervention at adequate strength/dosage for a sufficient length of time [2]. Terms 'refractory', 'intractable', 'drug-resistant', 'pharmaco-resistant' have been used interchangeably in several documented literature in different time periods [1]. Another major problem is problem in compliance of drugs, which arises due to many factors like education, poverty, inadequate knowledge about epilepsy etc. It results in 'pseudo' or 'apparent' refractoriness and more seen in developing countries. It must be excluded before the diagnosis of refractory epilepsy.

Table-1: (scale and factors)

Scale of refractoriness definitions

- **Potential** (no seizure freedom with AEDs taken less than 1 year and predictive factors for refractoriness).
- **Probable** (no seizure freedom more than 1 year with at least 2 AEDs).
- **Definitely refractory**(catastrophic epilepsy or no freedom of seizure for more than 1 year after 5 years of treatment with at least 3 AEDs).

Factors of refractoriness

Potential prognostic factors causing refractoriness identified in some studies include[1-8]:

Epileptic syndrome
Response to previous AEDs
Age
Seizure type and frequency
Structural cerebral abnormalities
Electroencephalography

Epileptic syndrome

In a study of a cohort of children with epilepsy followed up for over 30 49% of patients with symptomatic partial epilepsy and of all patients with idiopathic generalized epilepsy were refractory. Some epilepsy of childhood and epileptic syndromes are especially found to be treatment resistant [4]. 13% with idiopathic generalized epilepsy, and no case with idiopathic partial epilepsy, were refractory [5-8].

Response to previous AEDs

In syndrome, the probability of having a good response to treatment is inversely proportional to the numbers of drugs to which a patient has previously not responded. Absence of seizure freedom in two AEDs proved inefficient is a major predictor of refractoriness. A recent study showed 61% seizure freedom with the first AED, which decreased to 41% when first AED was not effective and second AED added and to 16% or less when previous 2 AEDs proved inefficient[6].

Age

A younger age at onset of epilepsy increases chance of refractoriness. Seizures in the immature brain contribute to high numbers of gap junctions. This causes abnormal connectivity, the hyper connected cortex leading to more epileptogenicity [7,8].

Seizure type and frequency

Different seizures respond differently to the available major AEDs. There are certain types of seizure which when present may predict future refractoriness. High seizure frequency (> 1 episode of seizure/month) after the diagnosis of epilepsy after treatment onset correlates with refractoriness [8].

Structural cerebral abnormalities

Localisation of the epileptogenic zone and structural cerebral abnormalities play important role in refractoriness. The temporal lobe is most epileptogenic area because it is the most common of the focal epilepsy syndrome. Cortex is another area with low seizure thresholds [8-10].

Electroencephalography (EEG)

EEG is useful for predicting refractoriness. The numbers of interictal spikes is predictive of severity in temporal lobe epilepsy. Patients with less than 1 spike per hour, correlate with less severe epilepsy. Some studies depict association between multifocal spikes and intractability [11].

History of febrile seizures

History of febrile seizure or febrile status is a definite risk factor. It's an aetiology of mesial temporal sclerosis causing refractory epilepsy [8].

AETIOLOGY [1, 11-15]

The causes of refractory epilepsy are numerous. (Table 2) Adverse peri-natal events (48 %) and CNS infections (24 %) top the list in a study by Chawla *et al*. [16]. Indian demography differs significantly from western [1].

CLINICAL FEATURES [1, 9, 16]

In refractory epilepsy the role of perfect history and presentation is much significant. The approach depends upon age of onset, accurate description: pre-ictal, ictal, post-ictal events, precipitating events, seizure types, evolution relation to fever previous history of febrile seizures (simple/complex), associated non-epileptic events, intake of AEDs with dose, developmental history, sleep history, detailed birth and peri-/antenatal history etc. Clinical examination depends upon anthropometry, syndromic facial dysmorphism, neurocutaneous features and detailed neurological and systemic assessment.

EVALUATION

Establish the diagnosis of epilepsy: RE can only be diagnosed on an individual basis. Pseudo-refractoriness indicates a condition in which seizures persist because the condition has not been adequately treated. The most common causes of pseudo refractory epilepsy include [17, 18]:

Inappropriate diagnosis
Bad compliance
Incorrect drug
Inadequate dosage
Inappropriate lifestyle

EEG

Routine EEG is a must for the clinical diagnosis of epilepsy and associated syndrome. For the majority of patients with epilepsy, routine EEG is sufficient to classify seizure type and to start treatment [19, 20]. But for RE and a doubtful seizure, video-EEG monitoring is the best diagnostic tool available. Continuous video and EEG monitoring over time helps in better way [21].

MRI

High-resolution MRI helps in isolating the cause of focal epilepsies and to predict long-term outcome and spontaneous remission in patients. Hippocampal volumetry, 3T MRI, Diffusion tensor imaging, etc., have revolutionised the management of epilepsy [22, 23].

Functional neuroimaging

This includes ictal and interictal SPECT, PET, fMRI and MRS. Interictal SPECT is most useful in temporal lobe epilepsy (TLE), and hypoperfusion means the region of seizure onset. In ictal SPECT hyperperfusion indicates seizure onset [22-25].

PET

An ictal FDG-PET is obtained in a patient with several epigastric auras during the 10 minutes following FDG injection which shows a clear-cut left mesial temporal glucose hypermetabolism. FDG-PET can identify MRI-negative medial TLE but less helpful in neocortical epilepsy. FMRI is being used for localizing the primary motor cortex. MRS may be useful in patients who have otherwise normal MRI. FDG-PET demonstrates right mesial temporal and temporo-polar hypometabolism, whereas FMZ-PET abnormality is restricted to the mesial temporal structure [26].

Table-2: (etiology)

Epilepsy syndromes	**Structural Abnormality**
Neonatal period Ohtahara syndrome Early myoclonic encephalopathy (EME) **Infancy** Epilepsy of infancy with migrating focal seizures West syndrome Dravet syndrome Doose syndrome **Childhood** Lennox-Gastaut syndrome Epilepsy with Myoclonic-Astatic epilepsy Epileptic encephalopathy with continuous spike and wave during sleep (CSWS) (including landau-kleffner) **Metabolic** Pyridoxine dependent epilepsy Biotinidase, GLUT1, Creatine, Serine biosynthesis deficiency Organic acidemia Urea cycle disorders Non-ketotic hyperglycinemia Aminoacidopathies Peroxisomal disorders Molybdenum cofactor deficiency, sulfite oxidase deficiency Mitochondrial disorders including Alpers syndrome Menkes disease GABA neurotransmitter defects Congenital disorders of glycosylation Progressive myoclonic epilepsies Hashimoto encephalopathy **Fever-related epilepsies:** Febrile infection-related epilepsy syndrome (FIRES), Idiopathic hemiconvulsion-hemiplegia syndrome(HHE) **Connective tissue disorders** Systemic lupus erythematosus, Wegener's granulomatosis, sarcoidsosis, celiac disease, Crohn's disease, Behcet's Sjorgren's syndrome,	*Malformations*:Neuronal migration defects and neural tube defects *Neurocutaneous syndromes*: Tuberous Sclerosis complex (TSC), Neurofibromatosis Type 1(NF1) Sturge Weber syndrome, Hypomelanosis of Ito, Incontinentia pigmenti, Epidermal nevus syndrome, *Infectious/Inflammatory*:Post meningitis/ meningoencephalitis/ encephalitis epilepsy, Hypoxic ischemic encephalopathy, Rasmussen encephalitis *Stroke* *Tumors* *Mesial temporal sclerosis* **Autoimmune epilepsies**: N-methyl-D-aspartate receptor(NMDAR), voltage gated potassium channel [VGKC]-complex, leucine rich glioma inactivated 1 [LGI1], glutamic acid decarboxylase (GAD) **Genetic** *Syndromic: Pitt Hopkins syndrome, Mowat Wilson syndrome, PEHO* *syndrome* *Chromosomal*

Metabolic Work up

Several metabolic screening tests are needed to rule out the metabolic diseases. It depends upon several clinical pointers [1].

Genetic Testing

The presence of features like dysmorphism, growth retardation, intellectual disability and hypotonia may indicate an underlying genetic syndrome [1,27],

Neuro-psychological evaluation

Neuropsychological testing gives an estimate of intellectual functioning and helps localising areas of the brain that are abnormal. Memory testing can help lateralise dysfunction to hemisphere. E.g., Low scores on verbal memory tests are s/o dominant temporal lobe and non-verbal memory impairment suggests non-dominant temporal lobe involvement.

TREATMENT

Risks and benefits of a curative or palliative surgical procedure or experimental therapy have to be weighed against the chance of improvement & side-effects of additional medical therapy. Medical refractoriness is no longer a prerequisite for surgery, if surgically remediable lesional epilepsy syndrome is found, surgical intervention should be planned, and in other conditions optimisation of pharmacotherapy should be considered. A systematic protocol for treatment of RE using a new AED might improve seizure control in a substantial proportion of cases. The nihilistic view that intractability is inevitable if seizure control is not obtained within a few years of the onset of therapy is incorrect. In RE, it is convenient to perform a systematized management be AED i.e, increase until the maximum tolerable dose. If no response, replace the AED; if there is a partial response; add another AED which should be chosen based on the action of the first AED, its efficacy and adverse effects.

Table-3: (Therapies)

Pharmacotherapy Old and new AED depending upon types of seizure [1, 28]. **Metabolic Treatment** biotin, pyridoxine, pyridoxal phosphate and folinic acid - all neonates with refractory seizures[1] **Epilepsy Surgery** curative (definitive) - resection of the epileptogenic focus Palliative- reducing the intensity and/ or the frequency of a certain seizure type [1, 29].	**Role of Diet[30]** The ketogenic diet (KD)- high fat, low carbohydrate, and restricted protein diet **Vagus Nerve Stimulation (VNS)[31]** **Deep Brain Stimulation (DBS)[32]** **Transcranial magnetic stimulation[33]** **Responsive neurostimulation[34]** **Optogenetics[35]** **Cerebral cooling[36]** **Local AED perfusion to the epileptogenic foci[1]** **Seizure prediction devices[37]** **Gene therapy[38]** **Stem cell based therapy[39]**

CONCLUSION

The refractory epilepsy is one of the commonest sources of morbidity in children with epilepsy. A detailed clinical evaluation with search for an underlying cause must be done. Rational and timely use of antiepileptic drugs, early referral of potential candidates for epilepsy surgery and early consideration for dietary non-pharmacological options are needed. A proportion of the economic and social cost of epilepsy is due to patients with seizures, are not controlled by standard medical therapy. There are many approaches, however, to treat their refractory conditions. Surgical treatment for epilepsy remains the best of all accepted medical treatments.

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