Indian J Pediatr (October 2014) 81(10):1063–1072
DOI 10.1007/s12098-014-1533-1

REVIEW ARTICLE

Refractory Epilepsy in Children

Satinder Aneja · Puneet Jain

Received: 3 March 2014 / Accepted: 2 July 2014 / Published online: 9 August 2014

Abstract Refractory epilepsy, estimated to affect 10–20 % children with epilepsy, can have profound effect on the education, social and cognitive functioning and recreational activities of the child. The definitions are still evolving. A detailed clinical evaluation may reveal an accurate syndromic and etiological diagnosis. The recent advances in neuroimaging and electrophysiology have revolutionized the management of children with refractory epilepsy and supplement the clinical evaluation. Genetic and metabolic evaluation may be indicated in selected cases. The rational use of anti-epileptic drugs, epilepsy surgery and dietary therapies are the mainstay in the management. Various experimental treatment options and pharmacogenetics offer hope for future.

Keywords Refractory epilepsy · Intractable epilepsy · Polytherapy · Epilepsy surgery · Dietary therapy

Introduction

Approximately 10–20 % children with epilepsy develop drug-refractory epilepsy. The identification of refractory epilepsy can have broad implications regarding education, social functioning and recreational activities of the child. This review briefly discusses the definition, mechanisms, investigations and treatment modalities available for a child with refractory epilepsy.

S. Aneja (✉) · P. Jain
Department of Pediatrics, Lady Hardinge Medical College and Associated Kalawati Saran Children's Hospital, New Delhi 110001, India
e-mail: drsaneja@gmail.com

P. Jain
Division of Pediatric Neurology, Department of Pediatrics, BLK Super Speciality Hospital, Pusa Road, New Delhi, India

Definition

Terms 'refractory', 'intractable', 'drug-resistant', 'pharmaco-resistant' have been used interchangeably in literature. Broadly, refractory epilepsy may be defined as failure of complete or acceptable control of seizures in response to the anti-epileptic drugs. Although many studies have used various definitions of refractory epilepsy [1–6], the definition is still evolving [7]. The consensus regarding the number of drug failures appeared to be 2–3 but the reported criteria for the seizure frequency were variable.

Recently, International League against Epilepsy (ILAE) proposed a consensus definition for drug-resistant epilepsy [8]. However, for routine use, failure of seizure-control despite trial of three appropriate anti-epileptic drugs (AED) regimens at maximum tolerated doses should be considered as drug-refractoriness and is highly likely to indicate failure with subsequent AED trials.

Another important concern is '*pseudo*' or '*apparent*' refractoriness. It should be excluded before a diagnosis of refractory epilepsy. The factors to be considered includes appropriateness of the drug for the epilepsy syndrome, compliance, 'seizure mimickers', adequate dosing and trial and drug interactions [9, 10].

Epidemiology

The refractory epilepsy is seen in 9–23 % of children with epilepsy [3, 11, 12]. Few studies have also explored the factors which may predict intractability [3, 11, 13]. Younger age at onset, [13–15] neonatal status epilepticus, [11, 13, 16] high initial seizure frequency, [11, 13, 16] failure of response to first anti-epileptic drug, [17] specific epilepsy syndromes (infantile spasms, [13, 16] Lennox-Gastaut syndrome [13]), mixed seizure types, [13, 16] symptomatic/cryptogenic

Table 1 Common etiologies of refractory epilepsy in children

*Epilepsy syndromes**
Ohtahara syndrome
Early myoclonic encephalopathy
Epilepsy of infancy with migrating focal seizures
West syndrome
Dravet syndrome
Lennox-Gastaut syndrome
Epilepsy with Myoclonic-Astatic epilepsy
Epileptic encephalopathy with continuous spike and wave during sleep (CSWS)
Structural
Malformations: Lissencephaly, Neuronal heterotopias, Polymicrogyria and Schizencephaly, Focal cortical dysplasia, Hemimegalencephaly, Holoprosencephaly
Neurocutaneous syndromes: Tuberous Sclerosis complex, Sturge Weber syndrome, Hypomelanosis of Ito, Incontinentia pigmenti, Epidermal nevus syndrome
Infectious/Inflammatory: Post-meningitis/encephalitis epilepsy, Rasmussen encephalitis, Hypoxic ischemic encephalopathy
Stroke
Tumors: Dysembryoblastic Neuroepithelial tumor (DNET), ganglioglioma, low grade astrocytoma, hypothalamic hamartoma
Mesial temporal sclerosis
Metabolic
Potentially treatable
Antiquitin deficiency (Pyridoxine dependent epilepsy)
Biotinidase deficiency
GLUT1 deficiency syndrome
Creatine deficiency
Serine biosynthesis deficiency
Others
Organic acidemia
Urea cycle disorders
Aminoacidopathies
Peroxisomal disorders
Non-ketotic hyperglycinemia
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
Genetic
Chromosomal: 1p36 deletion, 4p syndrome, Ring chromosome 14 and 20, Inv dup 15 syndrome, Down syndrome, Angelman syndrome
Syndromic: Pitt Hopkins syndrome, Mowat Wilson syndrome, PEHO syndrome
Specific genes: *MeCP2, CDKL5, FOXG1, SLC25A22, SPTAN1, STXBP1, ARX, KCNJ11, SCN1A, SCN1B, SCN2A*
Miscellaneous
Fever-related epilepsies: Febrile infection-related epilepsy syndrome (FIRES), Idiopathic hemiconvulsion-hemiplegia syndrome
Autoimmune epilepsies: NMDA, VGKC complex, GAD
Reflex epilepsies
Connective tissue disorders

GAD Glutamic acid decarboxylase; *NMDA* N-methyl-d-aspartate; *PEHO* Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy syndrome; *VGKC* Voltage-gated potassium channel

*They have diverse etiologies

etiology, [11–16] history of febrile seizures, [12,13,15,] history of status epilepticus, [13, 14, 16] abnormal neurological status [13, 15, 16] and abnormal neuroimaging [13, 14] are important factors which may predict drug-refractoriness. EEG features like diffuse slowing and focal spike-wave discharges were also found to be independent predictors of intractability [14].

The natural history of childhood epilepsies is complex. The 'Refractoriness' may not be a permanent state. The focal epilepsies may show late onset of refractoriness as compared to epileptic encephalopathies and other secondarily generalized epilepsies which show early drug refractoriness [3, 4, 15].

Etiology

The etiologies of refractory epilepsy in children are diverse. Table 1 lists the common etiologies of refractory epilepsy. In developing countries like India, the etiology of refractory epilepsy may differ from the western literature. The adverse peri-natal events (48 %) and CNS infection sequalae (24 %) were the major causes of refractory epilepsy in a study by Chawla et al. [18].

The search for an underlying etiology is pivotal as it may guide the medical or surgical treatment of the child and also aid in parental counseling.

The identification of a particular epilepsy syndrome is critical as it has implications for management and counseling [19]. For example, epileptic spasms in a normal or a delayed infant with/without neuroregression and hypsarrhythmia/variants on EEG suggest West syndrome. Refractory polymorphic seizures (predominantly tonic) in 3–5 y age group with cognitive decline and characteristic EEG features (slow spike-wave discharges and paroxysmal fast activity) are characteristic of Lennox-Gastaut syndrome. An infant presenting with frequent febrile seizures (mainly clonic), with subsequent evolution to refractory multiple seizure types (myoclonic/absences/focal) with neurocognitive deterioration, may have Dravet syndrome. The use of appropriate anti-epileptic drugs with realistic seizure-control goals is warranted in these conditions.

Clinical Evaluation

The history and physical examination are the basic tools in the evaluation of a child with refractory epilepsy. Table 2 lists the salient points to be included in the clinical evaluation.

Investigations

Electroencephalography (EEG)

A prolonged scalp EEG recording in a child with refractory epilepsy is invaluable and often rewarding. The aims of the EEG recording are epilepsy syndrome classification (*e.g.*, Lennox-Gastaut syndrome, West syndrome), localization of the epileptogenic lesion (irritative or epileptogenic zones) in cases of focal epilepsy, diagnosis of non-convulsive status epilepticus (commonly seen in many catastrophic childhood epilepsy syndromes) and evaluate the suspected non-epileptic events which may contribute to 'pseudo' refractoriness. It is especially useful in neonates to evaluate suspected subtle seizures and non-epileptic paroxysmal movements like reactive myoclonus. Figure 1 shows the EEG features in two common epilepsy syndromes.

The yield of the EEG recording can be increased by extending the duration of recording, inclusion of the video component or admitting for prolonged inpatient video-EEG monitoring (Long Term Monitoring; LTM). A sleep EEG recording is a must. The natural sleep is preferred but if sedation is required, it is prudent to record arousal at the end of the recording.

The scalp EEG has numerous limitations (*e.g.*, records activity only from the cerebral convexities, artefacts, signal decay). The invasive EEG recordings are used only when non-invasive methods (scalp EEG/neuroimaging) fail to localize the epileptogenic zone sufficiently or when the epileptogenic zone is very close to the eloquent cortex [20].

Table 2 Clinical evaluation of a child with refractory epilepsy

History
Age of onset of seizures
Accurate description of seizure: pre-ictal, ictal, post-ictal; precipitating events
Seizure types, evolution
Relation to fever
Previous history of febrile seizures (simple/complex)
Associated non-epileptic events
Anti-epileptic drugs: Names, dosages, duration, compliance, response, adverse effects
Developmental trajectory: normal, stagnation, regression
Pointers towards inborn error of metabolism (see later)
Co-morbidities (see later)
Sleep history
Detailed birth and peri-/antenatal history
Previous history of trauma/CNS infection
Examination
Anthropometry: Failure to thrive, Head circumference
Facial dysmorphism
Neurocutaneous features
Detailed neurological and systemic assessment

Neuroimaging

The advances in neuroimaging have revolutionized the management of pediatric epilepsy. The detailed discussion of the newer imaging modalities is beyond the scope of this article and has been reviewed recently [21–23].

The role of computed tomography (CT) head is limited. It may aid in diagnosis of disorders like neurocysticercosis, intra-uterine infections, neurocutaneous syndromes like Sturge Weber syndrome and Tuberous Sclerosis complex and tumors like Dysembryoplastic Neuroepithelial Tumors (DNET).

Magnetic Resonance Imaging (MRI) of the brain is the modality of choice in the initial investigation of a child with refractory epilepsy. As per ILAE recommendations, [24] the following MRI sequences should be performed: thin slice (4–5 mm) volumetric T1-weighted gradient-recalled echo sequence, axial and coronal T2-weighted sequence, fluid attenuated inversion recovery (FLAIR) sequence and high resolution oblique coronal T2-weighted imaging of the hippocampus. Gadolinium contrast may be required where tumors, vascular malformations, inflammation or infectious etiologies are suspected on non-contrast studies. 3 T-MRI brain provides improved image signal-to-noise and contrast-to-noise ratios as compared to the conventional 1.5 T-MRI brain. It may increase the yield of neuroimaging [25, 26] and is especially useful in cases of suspected malformations of cortical development.

A systematic approach to the visual assessment of the MRI images is essential even in the presence of the obvious lesion as dual pathology (association of two potentially epileptogenic lesions, hippocampal and extrahippocampal) is not uncommon. Further, mild focal cortical dysplasia may be missed on structural imaging [23]. If the initial MRI brain was normal in a child with refractory epilepsy, a repeat MRI may be rewarding especially if the initial study was inadequate, was done at a younger age (immature myelination) or for disorders with progressive radiological findings like Rasmussen encephalitis.

Functional neuroimaging is warranted in cases with normal structural imaging or discordant radiological and clinico-EEG features. The functional imaging modalities may include Inter-ictal Positron Emission Tomography (PET), Ictal and Inter-ictal Single-photon emission CT (SPECT), Subtraction

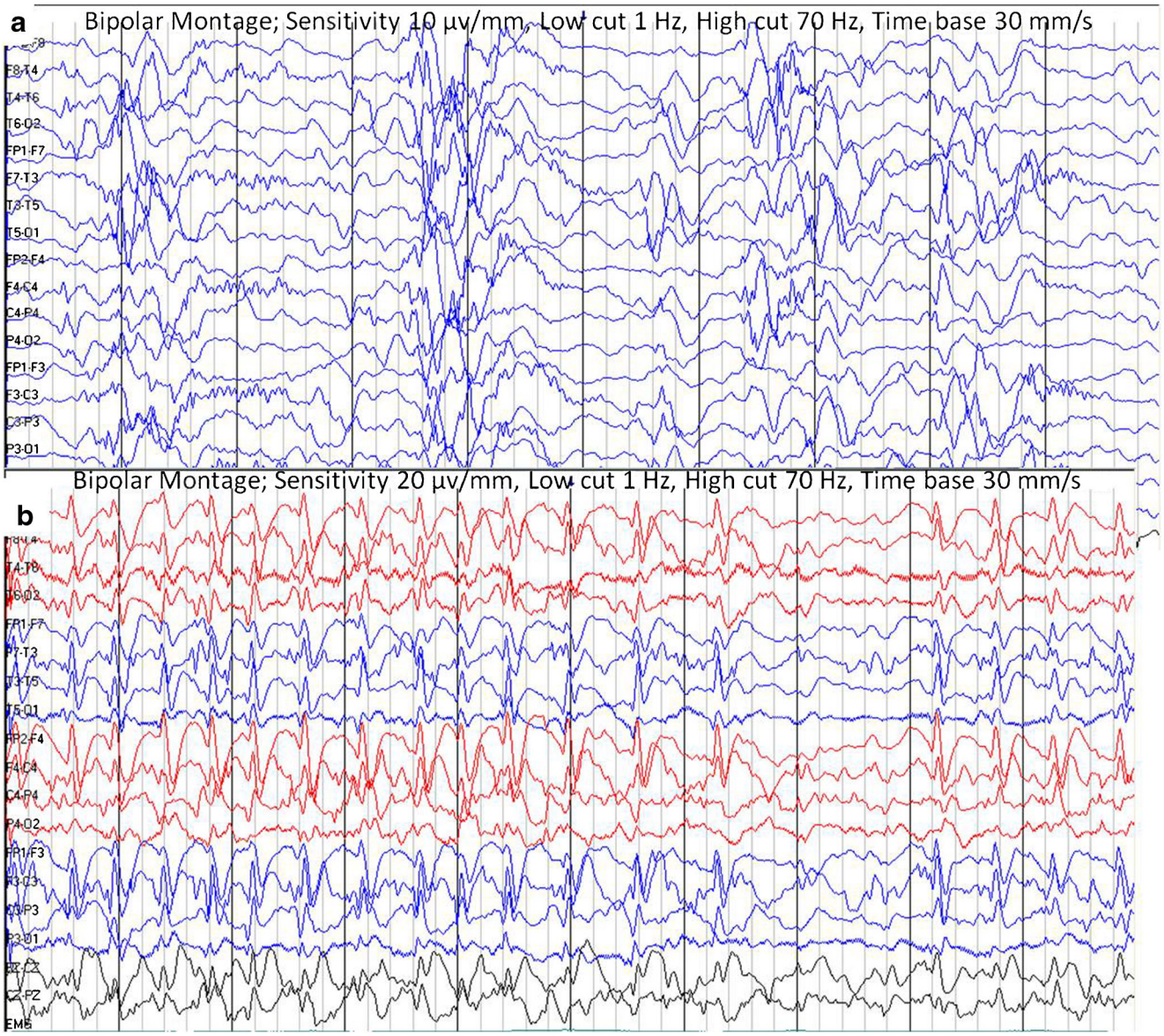

Fig. 1 EEG in refractory epilepsy. **a** – Modified hypsarrhythmia in West syndrome: The sleep record shows bursts of generalized synchronous and asynchronous high amplitude slow waves interspersed with spikes followed by electro-decremental response; **b** – EEG findings in epileptic encephalopathy with continuous spike and wave during sleep: there is nearly continuous 1–2 Hz bilateral synchronized spike wave discharges during the sleep

SPECT, SISCOM, Magnetoencephalography (MEG), Functional MRI, Simultaneous EEG and Functional MRI (EEG-fMRI) or Optical imaging. The detailed discussion of the functional imaging and other pre-surgical work-up is beyond the scope of this article.

Metabolic Work up

Refractory seizures may be seen in diverse neurometabolic disorders (Table 1). The epileptogenesis in these disorders may be secondary to lack of energy, intoxication, impaired neuronal function, disturbances of the neurotransmitter system or associated cerebral malformations.

Several clinical pointers (Table 3) may direct the pediatrician to investigate for a metabolic disorder. The metabolic work-up may also be warranted in children planned for dietary therapies.

The metabolic screen should include blood gas analysis, arterial lactate, blood sugar, ammonia and urinary ketones. Further investigations should be guided by the clinical suspicion. These may include tandem mass spectroscopy, urine gas chromatography–mass spectrometry, long chain fatty acids (peroxisomal disorders), urine mucopolysaccharides/oligosaccharides, urine sulphite test (sulphite oxidase deficiency), enzyme assays for lysosomal disorders, plasma/urine creatine, transferrin isoelectrophoresis (congenital

Table 3 Clinical clues towards an inborn error of metabolism in children with refractory epilepsy

Associated global developmental delay
Associated movement disorder – Creatine deficiency, organic acidemia
Worsening of seizures before meals – GLUT1 deficiency
Vomiting – urea cycle disorders
Abnormal urine odor – Maple syrup urine disease, phenylketonuria
Accelerated growth (macrosomia, tall stature) – GABA transaminase deficiency
Facial dysmorphism – Zellweger syndrome
Hair and skin abnormalities – Menkes disease, biotinidase deficiency
Albinism - Phenylketonuria
Dislocated lens – Sulphite oxidase deficiency
Inverted nipples, abnormal fat pads - Congenital disorders of glycosylation
Organomegaly, Coarse facies – Storage disorders
Multi-system involvement – Mitochondrial disorders, Congenital disorders of glycosylation, Peroxisomal disorders

disorders of glycosylation), serum copper and ceruloplasmin (Menkes disease), CSF sugar, lactate and neurotransmitter profile, skin and muscle biopsies.

Genetic Testing

The presence of suggestive features like dysmorphism, microcephaly, growth retardation, intellectual disability and hypotonia may indicate an underlying genetic syndrome. Currently, the genetic testing is most useful for Dravet and related syndromes, infantile spasms without any obvious etiology, epilepsy with brain malformations, epilepsy with intellectual disability or dysmorphism [27]. No useful tests are yet available for the most generalized and focal onset epilepsy syndromes.

The standard karyotype can detect alterations in chromosomal structure (deletion, duplication, translocation, inversions) or chromosome number (monosomies, trisomies). Fluoroscent in-situ hybridization (FISH) can identify presence, absence or rearrangement of specific DNA segments. It can detect deletion as small as 1 Mbp. Testing for the specific genes (Table 1) should be directed by the suspected epilepsy syndrome. Newer sensitive techniques [28] like Comparative genomic hybridization (CGH), Single nucleotide polymorphism (SNP) arrays, Multiplex ligation-dependent probe amplification (MLPA) and sequencing may aid to identify the underlying causes of 'idiopathic' epilepsies. 'Molecular' karyotyping (evaluation of chromosome content and structure using DNA hybridization) has led to the discovery of copy number variants (CNVs) associated with epilepsy. The three most common recurrent CNVs at 15q13.3, 16p13.11, and 15q11.2 have been established as substantial risk factors for epilepsy [29].

Treatment

The goals of treatment of children with refractory epilepsy include 'realistic' seizure control with minimal adverse effects of the administered drugs with improvement in overall quality of life. This should be coupled with early identification of potential candidates for non-pharmacological therapies. The treatment revolves around three modalities: pharmacotherapy, epilepsy surgery and alternative measures (like dietary therapy, vagus nerve stimulation).

Pharmacotherapy

The decision to start a particular anti-epileptic drug is largely empirical and rarely evidence-based. The selection should be based on the patients' characteristics (age, sex, co-morbidities, co-medications), seizure type or epilepsy syndrome, previous responses and adverse effects to AEDs and the expected response from the remaining untried drugs. A realistic goal with regard to seizure reduction should be set and 'overtreatment' (unnecessary or excessive AED load in the management of epilepsy leading to a suboptimal risk-to-benefit ratio) [30] be avoided. Various new AEDs [31, 32] have flooded the market with many more antiepileptogenesis targets being explored [33].

Polytherapy

Monotherapy with anti-epileptic drugs (AEDs) is often desirable. But as noted earlier, about a third of patients with epilepsy will be drug-refractory, polytherapy with the anti-epileptic drugs is often unavoidable. The main goal of polytherapy is to achieve realistic seizure control (total elimination or seizure reduction based on the etiology) with minimal adverse effects and least impact on the quality of life.

Irrational polytherapy may result from inadequate knowledge of the mechanisms of action of various AEDs, their pharmacokinetic and pharmacodynamic interactions, inappropriate diagnosis of epilepsy syndrome with use of inappropriate AED and unrealistic seizure reduction goals.

It is often prudent to combine drugs with different mechanisms of action.

Pharmacokinetic interactions are the effects of drugs upon the disposition of one another, including changes in absorption, metabolism, protein binding, and excretion. The most clinically relevant interactions are the ones affecting the drug metabolism. The hepatic cytochrome P450 enzyme system metabolizes the majority of the AEDs. These drugs can induce (phenobarbitone, phenytoin, carbamazepine), inhibit (valproate) or have minimal or no effect (levetiracetam, lamotrigine, topiramate, oxcarbamazepine, zonisamide) on these enzymatic pathways. These interactions have profound

effect on the treatment efficacy and adverse effect profile of a polytherapy regimen.

Further, an appropriate diagnosis of the epilepsy syndrome is pivotal for the pharmacotherapy with use of appropriate AEDs. Phenobarbitone, phenytoin, carbamazepine, vigabatrin and gabapentin may exacerbate absence and myoclonic seizures (including epileptic spasms). Benzodiazepines may worsen tonic seizures. Carbamazepine and lamotrigine may worsen Electrical status epilepticus during sleep (ESES) spectrum epilepsies.

Convincing evidence to guide the pediatric neurologist/pediatrician on when and how to combine AEDs is still insufficient, and the current practice recommendations remain largely empirical. Table 4 shows some rational drug combinations [34–36].

Few guiding tips for polytherapy includes: Adequate trial of a single AED (dose and duration), combine drugs with different mechanisms of action, inclusion of at least one broad spectrum AED in the regimen, avoiding combination of drugs with prominent sedative effects, trial of different dual drug therapies before adding a third drug, slow titration of a new drug, reduction of the dose of the older drug once the goal of seizure reduction is achieved with the new drug and exclusion of the causes of 'pseudo' refractoriness. Always consider non-pharmacological options of treatment as children who have failed the first anti-epileptic drug, are less likely to respond to subsequently added drugs [17, 37, 38].

Treatment of Non-Convulsive Status Epilepticus (NCSE)

NCSE may be commonly seen in some epilepsy syndromes [like Lennox-Gastaut-syndrome (LGS), Doose syndrome, Dravet-syndrome, *etc*.]. Oral or intravenous benzodiazepines are usually the first step. It is to be noted that benzodiazepines may precipitate tonic status in children with LGS and hence should be used with caution. Oral steroids, intravenous pulsed methylprednisolone or adrenocorticotrophin hormone may be tried in children who fail treatment with benzodiazepines. Carbamazepine, phenytoin and phenobarbitone must be avoided in these situations.

Table 4 Rational drug combinations

Valproate-Lamotrigine for absence and myoclonic seizures
Valproate-Ethosuximide for absence seizures
Levetiracetam-Lacosamide
Levetiracetam- Lamotrigine
Stiripentol-Clobazam for Dravet syndrome
Phenytoin-Phenobarbitone
Lamotrigine-Topiramate
Vigabatrin-Tiagabin for focal seizures

Metabolic Treatment

Empiric trials of biotin, pyridoxine, pyridoxal phosphate (not available in India) and folinic acid should be considered in all neonates with refractory seizures. Other epilepsies responsive to metabolic treatment are shown in Table 5.

Therapeutic Drug Monitoring (TDM)

The routine monitoring of plasma concentrations is costly and does not add any useful information. The drug monitoring may be useful to assess compliance and to explain recent changes in seizure frequency or drug tolerability, particularly in children on polytherapy where the problematic drug is unclear. It may also be prudent to test children when changes in the drug pharmacokinetics are expected like with hepatic or renal failure or gastrointestinal problems affecting drug absorption [41].

The blood samples should be drawn at a steady state, which occurs at 4–5 half lives after treatment initiation or dose modification. The ideal sampling time for all AEDs is drug fasting in the morning [41]. If drug toxicity is suspected, then one sample is drawn at the time of the trough and the second sample at the time of suspected concentration-related symptoms.

Epilepsy Surgery

Epilepsy surgery can be performed effectively and safely in young children. It often results in reduction in seizure frequency/seizure freedom, improvement in quality of life and probably reversal of developmental stagnation. With over 500,000 potential epilepsy surgery candidates in India, not more than 200 epilepsy surgeries per year in handful of centers are being performed today [42].

As per ILAE guidelines, [43] the potential candidates for epilepsy surgery evaluation include children with uncontrolled [8] or disabling (including medication side effects) seizures, children with epilepsies that cannot be assigned to

Table 5 Epilepsies responsive to metabolic treatment [39, 40]

Ketogenic diet: GLUT1 deficiency syndrome
Biotin (10–100 mg/d): Biotinidase deficiency, Holocarboxylase synthetase deficiency
Folinic acid (3–5 mg/kg/d): Antiquitin deficiency (*ALDH7A1* mutation)
Pyridoxine (15–30 mg/kg/d): Antiquitin deficiency (*ALDH7A1* mutation)
Pyridoxal phosphate (30 mg/kg/d): Pyridoxamine-phosphate oxidase (PNPO) deficiency, Antiquitin deficiency (*ALDH7A1* mutation)
Creatine (300–400 mg/kg/d): Guanidinoacetate methyltransferase (GAMT) deficiency
L-Serine (300–500 mg/kg/d): Serine deficiency

an electro-clinical syndrome but with stereotyped, lateralized or focal seizures or in whom the MRI reveals a lesion amenable to surgical removal.

The detailed pre-surgical evaluation is beyond the scope of this article. It includes EEG, structural and functional neuroimaging and neuropsychological testing. The various surgical procedures available are shown in Table 6. There is a need to identify the potential candidates early with prompt referral to an epilepsy surgery centre.

Role of Dietary Therapies

The ketogenic diet (KD) is a high fat, low carbohydrate, and restricted protein diet and is an effective non-pharmacological treatment for refractory epilepsy [44–47]. It should be considered earlier as an option for treatment of drug-refractory epilepsy. It is specifically the treatment of choice for GLUT1 deficiency syndrome and pyruvate dehydrogenase deficiency. The contraindications are few and include mitochondrial β-oxidation defects, primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, pyruvate carboxylase deficiency and porphyria. It is usually well tolerated and the adverse effects may include gastrointestinal (vomiting, constipation, diarrhea, abdominal pain), hyperuricemia, hypocalcemia, acidosis, renal calculi, growth retardation and prolonged QT interval [48].

More liberal varieties of the classical KD have been developed and these include Modified Atkins Diet, Low glycemic index diet and Medium Chain Triglyceride (MCT)-KD. They have an efficacy close to the classical KD [49].

Table 6 Epilepsy surgery – Therapeutic procedures

Temporal and extra-temporal resections
Hemispherectomy and Hemispherotomy (less aggressive)
May be indicated in children with refractory epilepsy with severe hemiparesis and no remaining useful hand function; usual indications include Rassmussen's encephalitis, Sturge Weber syndrome and rarely cortical dysplasias
Gamma knife radio-surgery
Usual indications: cavernomas, hypothalamic hamartoma
Palliative procedures
Corpus callosotomy
Usually indicated for refractory symptomatic generalized epilepsies with multiple seizure types; especially used for tonic/atonic seizures in children with Lennox-Gastaut syndrome
Multiple sub-pial resections
Indications: Landau-Kleffner syndrome, patients with epileptogenic zone within the eloquent cortex

Neurostimulation

Vagus Nerve Stimulation (VNS) therapy stimulates the left vagus nerve. The impulses ascending along the vagus nerve reach the nucleus of tractus solitaries with subsequent spread to limbic, reticular and autonomic regions and brainstem nuclei, which may influence various neurotransmitter systems [50]. The optimal VNS settings are still unknown. VNS may be considered as adjunctive treatment for children with refractory partial or generalized epilepsy if they are poor surgical candidates or have had unsuccessful surgery [51]. Its complications are uncommon and minor and may include infections, lead fractures, throat discomfort, hoarseness, coughing, increase in drooling or dysphagia and sleep apnea.

Deep Brain Stimulation (DBS) uses chronic electrical stimulation applied to deep nuclei with widespread connections [50]. Centromedian and anterior nucleus of thalamus have been used as targets for DBS in refractory epilepsy patients.

Latest Advances

Despite recent advances in AEDs research, encouraging results with epilepsy surgery, and resurgence of dietary therapies, seizure freedom in children with refractory epilepsy is a distant reality. Thus, novel approaches to treat epilepsy are highly needed. Table 7 lists the new therapeutic options for treating refractory epilepsy.

Comprehensive Care

A multidisciplinary team comprising of pediatrician/pediatric neurologist, psychologist, rehabilitation, ophthalmologist, ENT specialist, trained nursing, dietician, social worker and public support, is required for the comprehensive care of children with refractory epilepsy. There is a profound impact on the social functioning, education and recreational activities.

Table 7 New therapeutic options for treating refractory epilepsy [50, 52–54]

Optogenetics
Transcranial magnetic stimulation
Responsive neurostimulation
Cerebral cooling
Local AED perfusion to the epileptogenic foci
Seizure prediction devices
Gene therapy
Stem cell based therapy

The periodic screening for various co-morbidities like tone abnormalities, contractures, vision/hearing deficits, dental hygiene, difficulty in feeding/malnutrition, sleep disorders and behavioral disorders, and adverse effects of the anti-epileptic drugs is warranted. The compliance with the drug therapy is to be emphasized. The triggering factors (*e.g.*, sleep deprivation, fever, trauma) should be avoided if possible. There is no restriction on watching television or videogames provided the child sits at maximum distance possible from the screen and there is additional lighting in the room.

Children with epilepsy are believed to be at higher risk of incurring accidental injury than those without seizures. Supervision while sleeping and bathing is necessary. Swimming should be avoided till 3 mo of seizure freedom. Protective helmets may be recommended for poorly controlled generalized epilepsies to avoid head injuries. Children on long term AEDs especially phenobarbitone, phenytoin, carbamazepine and valproate should receive adequate vitamin D (400 IU/d) and calcium. Periodic screening of serum 25 (OH) vitamin D should be considered.

Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP [55] is rare in children with epilepsy [56, 57]. The adult studies have identified many risk factors for SUDEP and include high seizure frequency especially generalized tonic-clonic seizures, polytherapy, early onset of epilepsy (<15 y) and associated intellectual disability [58]. SUDEP is not easy to prevent especially in children with refractory epilepsy. The rational use of AEDs and early referral for non-pharmacological modalities would be prudent.

Pharmacogenetics and Epilepsy

Pharmacogenetics refers to the science about how genetic variations affect the drug metabolism, drug targets or disease pathways leading to varying response to the drug with regard to its efficacy or adverse effect profile. The three important categories of candidate genes which may influence AED

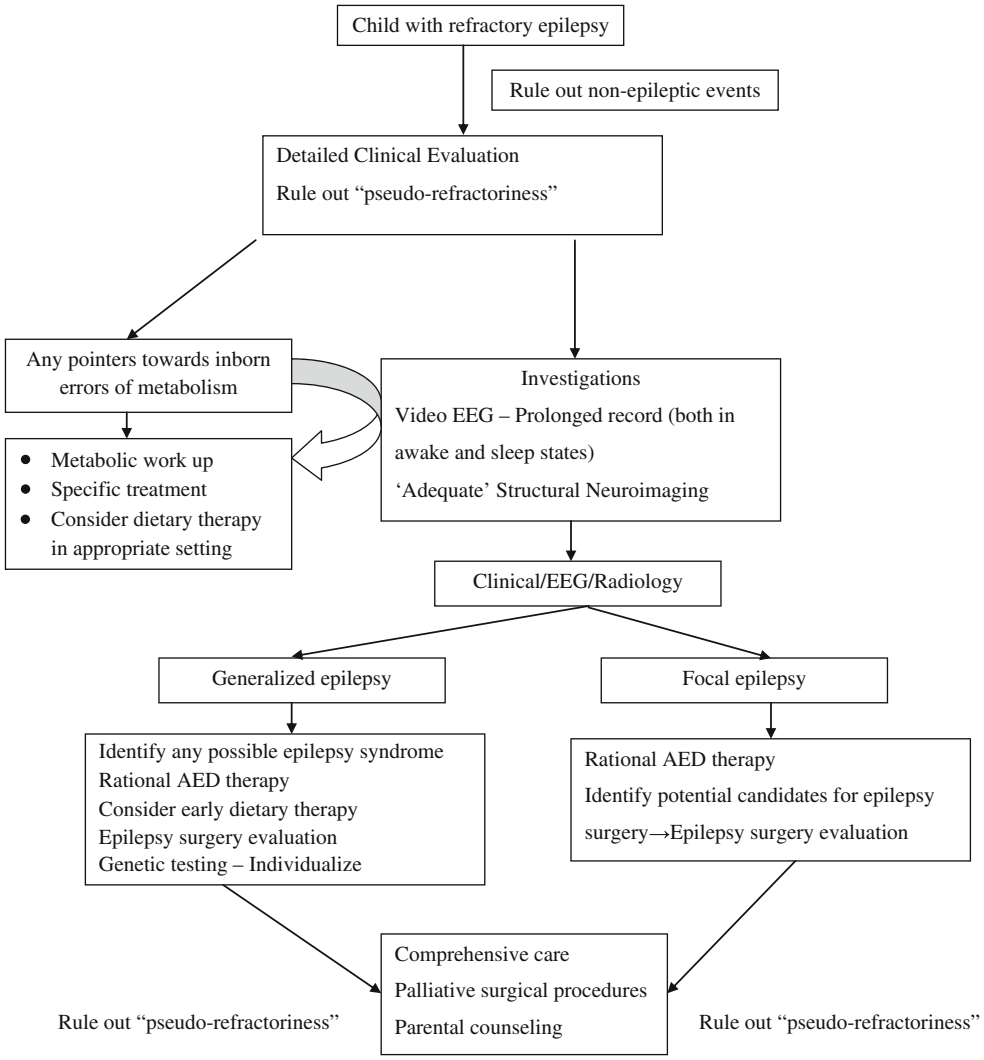

Fig. 2 Approach to a child with refractory epilepsy

response are genes encoding the drug transporters, metabolizing enzymes and AED targets [59].

Among the drug transporters, majority of the work has focused on MDR1 (Multidrug-Resistance protein1) (*ABCB1*). A recent meta-analysis found no significant association of *ABCB1* alleles, genotypes and haplotypes with the response to AEDs in the patients with epilepsy [60]. The cytochrome 450 enzyme system has been extensively studied among the drug metabolizing enzymes. A limited number of reliable and robust associations have been identified. Low activity alleles of *CYP2C9* (*2 and *3) have been shown to be associated with lower dose requirements for phenytoin, higher plasma levels and increased toxicity [61, 62].

The main candidate genes encoding AED targets include those encoding ion channel subunits and elements of neurotransmitter pathways. The studies exploring these candidate genes are limited and have shown inconsistent results. Many recent papers have reviewed the potential of pharmacogenetics in the treatment of epilepsy [59, 63, 64].

Conclusions

The refractory epilepsy is a major source of morbidity in children. An approach to a child with refractory epilepsy is shown in Fig. 2. A detailed clinical evaluation followed by a meticulous search for an underlying etiology especially potentially treatable causes, is imperative. Rational use of antiepileptic drugs, early referral of potential candidates for epilepsy surgery and early consideration for non-pharmacological options like dietary therapies is warranted. Newer therapeutic options are exciting but require further development and clinical experience. The pharmacogenetics may improve our understanding of the refractory epilepsy and aid in devising rational therapeutic strategies.

Conflict of Interest None.

Source of Funding None.

References

1. Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. Ann Neurol. 1990;28:699–705.
2. Casetta I, Granieri E, Monetti VC, Gilli G, Tola MR, Paolino E, et al. Early predictors of intractability in childhood epilepsy: A community-based case–control study in copparo. Italy Acta Neurol Scand. 1999;99:329–33.
3. Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, et al. How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol. 2006;60:73–9.
4. Berg AT. Identification of pharmacoresistant epilepsy. Neurol Clin. 2009;27:1003–13.
5. Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: a case–control study. Epilepsia. 1996;37:24–30.
6. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. Neurology. 2001;57:2259–64.
7. Berg AT, Kelly MM. Defining intractability: comparisons among published definitions. Epilepsia. 2006;47:431–6.
8. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia. 2010;51:1069–77.
9. Sisodiya S. Etiology and management of refractory epilepsies. Nat Clin Pract Neurol. 2007;3:320–30.
10. Kossoff EH. Intractable childhood epilepsy: choosing between the treatments. Semin Pediatr Neurol. 2011;18:145–9.
11. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. Neurology. 2001;56:1445–52.
12. Geerts A, Arts WF, Stroink H, Peeters E, Brouwer O, Peters B, et al. Course and outcome of childhood epilepsy: a 15-y follow-up of the Dutch study of epilepsy in childhood. Epilepsia. 2010;51:1189–97.
13. Seker Yilmaz B, Okuyaz C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol. 2013;48:52–5.
14. Ko TS, Holmes GL. EEG and clinical predictors of medically intractable childhood epilepsy. Clin Neurophysiol. 1999;110:1245–51.
15. Geerts A, Brouwer O, Stroink H, van Donselaar C, Peters B, Peeters E, et al. Onset of intractability and its course over time: The Dutch study of epilepsy in childhood. Epilepsia. 2012;53:741–51.
16. Kwong KL, Sung WY, Wong SN, So KT. Early predictors of medical intractability in childhood epilepsy. Pediatr Neurol. 2003;29:46–52.
17. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
18. Chawla S, Aneja S, Kashyap R, Mallika V. Etiology and clinical predictors of intractable epilepsy. Pediatr Neurol. 2002;27:186–91.
19. Jain P, Sharma S, Tripathi M. Diagnosis and management of epileptic encephalopathies in children. Epilepsy Res Treat. 2013;2013:501981.
20. Noachtar S, Rémi J. The role of EEG in epilepsy: a critical review. Epilepsy Behav. 2009;15:22–33.
21. Salmenpera TM, Duncan JS. Imaging in epilepsy. J Neurol Neurosurg Psychiatr. 2005;76 Suppl 3:iii2–iii10.
22. Duncan JS. Imaging in the surgical treatment of epilepsy. Nat Rev Neurol. 2010;6:537–50.
23. Bernasconi A, Bernasconi N, Bernhardt BC, Schrader D. Advances in MRI for "cryptogenic" epilepsies. Nat Rev Neurol. 2011;7:99–108.
24. Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, et al; ILAE, Committee for Neuroimaging, Subcommittee for Pediatric. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009;50:2147–53.
25. Knake S, Triantafyllou C, Wald LL, Wiggins G, Kirk GP, Larsson PG, et al. 3 T phased array MRI improves the Presurgical evaluation in focal epilepsies: a prospective study. Neurology. 2005;65:1026–31.
26. Zijlmans M, de Kort GAP, Witkamp TD, Huiskamp GM, Seppenwoolde JH, van Huffelen AC, et al. 3 T versus 1.5 T phased-array MRI in the presurgical work-up of patients with partial epilepsy of uncertain focus. J Magn Reson Imaging. 2009;30:256–62.
27. Pal DK, Pong AW, Chung WK. Genetic evaluation and counseling for epilepsy. Nat Rev Neurol. 2010;6:445–53.
28. Pong AW, Pal DK, Chung WK. Developments in molecular genetic diagnostics: An update for the pediatric epilepsy specialist. Pediatr Neurol. 2011;44:317–27.

29. Mulley JC, Mefford HC. Epilepsy and the new cytogenetics. Epilepsia. 2011;52:423–32.
30. Raspall-Chaure M, Neville BG, Scott RC. The medical managementof the epilepsies in children: conceptual and practical considerations. Lancet Neurol. 2008;7:57–69.
31. Chu-Shore CJ, Thiele EA. New drugs for pediatric epilepsy. Semin Pediatr Neurol. 2010;17:214–23.
32. Prunetti P, Perucca E. New and forthcoming anti-epileptic drugs. Curr Opin Neurol. 2011;24:159–64.
33. Kobow K, Auvin S, Jensen F, Löscher W, Mody I, Potschka H, et al. Finding a better drug for epilepsy: antiepileptogenesis targets. Epilepsia. 2012;53:1868–76.
34. Brodie MJ, Sills GJ. Combining antiepileptic drugs–rational polytherapy? Seizure. 2011;20:369–75.
35. French JA, Faught E. Rational polytherapy. Epilepsia. 2009;50:S63–8.
36. Brigo F, Ausserer H, Tezzon F, Nardone R. When one plus one makes three: The quest for rational antiepileptic polytherapy with supraadditive anticonvulsant efficacy. Epilepsy Behav. 2013;27: 439–42.
37. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol. 2006;13:277–82.
38. Ramos-Lizana J, Aguilera-López P, Aguirre-Rodríguez J, Cassinello-García E. Response to sequential treatment schedules in childhood epilepsy: risk for development of refractory epilepsy. Seizure. 2009;18:620–4.
39. Wolf NI, García-Cazorla A, Hoffmann GF. Epilepsy and inborn errors of metabolism in children. J Inherit Metab Dis. 2009;32:609–17.
40. Wolf NI, Bast T, Surtees R. Epilepsy in inborn errors of metabolism. Epileptic Disord. 2005;7:67–81.
41. Johannessen SI, Landmark CJ. Value of therapeutic drug monitoring in epilepsy. Expert Rev Neurother. 2008;8:929–39.
42. Radhakrishnan K. Epilepsy surgery in India. Neurol India. 2009;57:4–6.
43. Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al; International League Against Epilepsy, Subcommission for Paediatric Epilepsy Surgery; Commissions of Neurosurgery and Paediatrics. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the subcommission for pediatric epilepsy surgery. Epilepsia. 2006;47:952–9.
44. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2012;3: CD001903.
45. Raju KNV, Gulati S, Kabra M, Agarwala A, Sharma S, Pandey RM, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. Epilepsy Res. 2011;96:96–100.
46. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7:500–6.
47. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia. 2009;50:1109–17.
48. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: Recommendations of the international ketogenic diet study group. Epilepsia. 2009;50: 304–17.
49. Miranda MJ, Turner Z, Magrath G. Alternative diets to the classical ketogenic diet–can we be more liberal? Epilepsy Res. 2012;100:278–85.
50. Kotagal P. Neurostimulation: vagus nerve stimulation and beyond. Semin Pediatr Neurol. 2011;18:186–94.
51. Morris GL 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013. doi:10.1212/WNL.0b013e3182a393d1
52. Fisher RS. Therapeutic devices for epilepsy. Ann Neurol. 2012;71: 157–68.
53. Stacey W, Le Van QM, Mormann F, Schulze-Bonhage A. What is the present-day EEG evidence for a preictal state? Epilepsy Res. 2011;97:243–51.
54. Sørensen AT, Kokaia M. Novel approaches to epilepsy treatment. Epilepsia. 2013;54:1–10.
55. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 2012;53:227–33.
56. Berg AT, Nickels K, Wirrell EC, Geerts AT, Callenbach PM, Arts WF, et al. Mortality risks in new-onset childhood epilepsy. Pediatrics. 2013;132:124–31.
57. Sillanpää M, Shinnar S. SUDEP and other causes of mortality in childhood-onset epilepsy. Epilepsy Behav. 2013;28:249–55.
58. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med. 2011;365:1801–11.
59. Depondt C. The potential of pharmacogenetics in the treatment of epilepsy. Eur J Paediatr Neurol. 2006;10:57–65.
60. Haerian BS, Lim KS, Tan CT, Raymond AA, Mohamed Z. Association of ABCB1 gene polymorphisms and their haplotypes with response to antiepileptic drugs: a systematic review and metaanalysis. Pharmacogenomics. 2011;12:713–25.
61. Ninomiya H, Mamiya K, Matsuo S, Ieiri I, Higuchi S, Tashiro N. Genetic polymorphism of the CYP2C subfamily and excessive serum phenytoin concentration with central nervous system intoxication. Ther Drug Monit. 2000;22:230–2.
62. Wang B, Wang J, Huang S-Q, Su H-H, Zhou S-F. Genetic polymorphism of the human cytochrome P450 2C9 gene and its clinical significance. Curr Drug Metab. 2009;10:781–834.
63. Löscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia. 2009;50:1–23.
64. Cavalleri GL, McCormack M, Alhusaini S, Chaila E, Delanty N. Pharmacogenomics and epilepsy: The road ahead. Pharmacogenomics. 2011;12:1429–47.