Review Article
Cent Asian J Med Sci. 2017 Feb;3(1): 4-10.
Central Asian Journal of Medical Sciences
CAJMS

Advanced Treatment of Intractable Childhood Epilepsy

Hye Eun Kwon[1], Heung Dong Kim[2]

[1]Department of Pediatrics, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea; [2]Division of Pediatric Neurology, Department of Pediatrics, Pediatric Epilepsy Clinic, Severance Children's Hospital, Epilepsy Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea

Corresponding Author
Heung Dong Kim, MD, PhD
Division of Pediatric Neurology, Department of Pediatrics, Pediatric Epilepsy Clinic, Severance Children's Hospital, Epilepsy Research Institute, Yonsei University College of Medicine, 134, Shinchon-dong, Seodaemun-gu, Seoul, 120-752, Republic of Korea
Tel: +82-2-2228-2061
Fax: +82-2-393-9118
E-mail: hdkimmd@yuhs.ac

Objectives: Up to one third of epilepsy patients have an unsatisfactory treatment with antiepileptic drugs (AEDs), but advance in neuroimaging, neurophysiologic investigation and treatment modalities have substantially improved the approaches and understanding of intractable childhood epilepsy. **Methods:** Journal papers, reports, books and government publications on epilepsy treatment were collected and reviewed in chronological order. **Results:** There are approximately more than 15 newer AEDs developed since 1990, highlighted by the novel mechanism of action with minimal adverse effect, thus they have been frequently used for those who are unresponsive to conventional AEDs. Non-pharmacologic therapies including diet therapy, epilepsy surgery, and neuromodulatory treatment are also effective and should be considered early in the disease course. Diet therapy began to reemerge in mid 1990s, and studies with large data collection allowed to overcome major concerns; its side effects, difficult compliance and doubts on efficacy. And more liberal forms of the diet therapy were introduced to benefit adults and patients in developing counties, where strict supervision is unavailable. The surgical treatment has become increasingly more valuable and it is now accepted for the management of drug resistant focal epilepsy due to major advances in presurgical investigation methods, and surgical techniques. **Conclusions:** The timely assessment of children with drug-resistant epilepsy and active application of advanced treatment modalities were necessary to prevent the effect of uncontrolled seizures on cognitive and behavioral development.

Keywords: Intractable Epilepsy, Diet Therapy, Neorosurgery

Introduction

Epilepsy is one of the most common chronic neurologic conditions in the world, affecting approximately 0.5 to 1% of the general population through the life. Of those newly diagnosed as epilepsy, approximately 70% are children under the age of 16 years. Medical management with antiepileptic drugs (AEDs) is considered first-line treatment, but up to one third of epilepsy patients have an unsatisfactory treatment outcome [1]. The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as 'failure of adequate trials of two tolerated and appropriated chosen and used AEDs schedules to achieve sustained seizure freedom' [2].

Pediatric group differs from other age groups in that they are

likely to have more complex and adverse course with medically refractory epilepsy [3]. In those cases, newer AEDs and nondrug therapy such as diet therapy and epilepsy surgery should be considered early in the disease course.

In this review, we focus on the advanced treatment modalities for intractable childhood epilepsy.

Newer antiepileptic drug

Traditionally, AEDs marketed before the 90's are defined as 'old' AEDs, while drugs that have been introduced after the 90's are considered as 'newer' AEDs. The noble development of AEDs has increased more rapidly since 1990, and there are approximately more than 15 newer agents. The newer AEDs was emphasized because these drugs had fewer adverse effects compared to old drugs. Although the newer agents lack longitudinal clinical experience, but the mechanism of action was well introduced, which help neurologists to choose and combine the drugs. We reviewed the mechanism and clinical application of the new drugs that are widely used in intractable childhood epilepsy.

Vigabatrin

Vigabatrin, the first 'designer drug', is a structural analogue of gamma aminobutyric acid (GABA), which irreversibly inhibits GABA transaminase, thus preventing the breakdown of GABA.

Indication: A first line drug for treatment of West syndrome in children with tuberous sclerosis [4, 5]. As there is insufficient evidence for the use of other AEDs for West syndrome, vigabatrin may be considered as a first line drug in patients with West syndrome for those who are contraindicated or restrticted hormonal treatment (corticosteroids, ACTH) [5].

Adverse effect: Visual field defects are the main concern. It occurs in around one-third of patients and is not usually reversible [6]. Vigabatrin was initially marketed for an add on treatment for focal epilepsy, but now its use has been limited to special situation [7].

Dosage: Start treatment with 50 mg/kg/day and adjust according to the response over 7 days, up to a total of 150 mg/kg/day.

Lamotrigine

The antiepileptic activity of lamotrigine is by inhibition of the sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Indication: Lamotrigine has proven to be effective adjunct in the treatment of many generalized and focal seizure types [8, 9]. It is at its best efficacy when combined with valproate due to their beneficial pharmacodynamics interactions.

Adverse effect: Skin rash occurs in about 10% of patients, but serious rashes leading to hospitalization, including Steven Johnson syndrome and toxic epidermal necrolysis, are less likely [10]. However, it is more often seen when co-administrated with valproate, exceeded the recommended initial dose, or titrated rapidly. Nearly all life threatening rashes occurs in the initiation of treatment within 2 to 8 weeks.

Pro-myoclonic effects may aggravate myoclonic jerks in juvenile myoclonic epilepsy, Dravet syndrome and progressive myoclonic epilepsies.

Dosage: Recommended dosing guidelines vary according to monotherapy, co-medication with valproate and co-medication with enzyme inducing AEDs.

Topiramate

Topiramate is multimodal AED acting on voltage dependent sodium channels, enhancing GABA, decreasing glutamate, and inhibiting carbonic anhydrase enzyme.

Indication: Topiramate is a highly efficacious adjunct in refractory focal or generalized epilepsy and peculiarly difficult-to-treat epileptic encephalopathies, such as West syndrome and Lennox-Gastaut syndrome (LGS) [11,12].

Adverse effect: Frequent reported adverse effects are dizziness, difficult with concentration/ attention, memory impairment, psychomotor slowing and speech disorders. More serious side effects include metabolic acidosis, nephrolithiasis, decreased sweating result in hyperthermia.

Dosage: Start dose with 0.5-1 mg/kg/day, and gradually increase to recommended maintenance dose 5-9 mg/kg/day.

Oxcarbazepine

Oxcarbazepine is similar to carbamazepine in its antiepileptic efficacy and main mechanism of action. It blocks voltage dependent ionic membrane conductance (especially sodium, potassium and calcium), resulting in stabilization of hyperexcited neural membranes and synaptic actions of neurotransmitter (e.g., GABA, glutamate); the effect is diminution of propagation of synaptic impulses. Oxcarbazepine has more favorable

pharmacologic and adverse event profiles, compared to carbamazepine.

Indication: Oxcarbazepine is a first class AED for monotherapy in focal epilepsies [13]. Adverse effect: Hyponatremia is common, but it infrequently leads to complication.

Dosage: Start dose with 10 mg/kg/day, increase to a maximum of 30-45 mg/kg/day for optimal dose.

Levetiracetam

Levetiracetam does not have a direct interaction with the three conventional mechanisms of the other AEDs: Na+, T-type Ca 2+ currents, and GABAergic system. It has a novel mechanism of action because it binds to a specific target called synaptic vesicle protein 2A in presynaptic terminals, which is an integral membrane glycoprotein involved in the control of vesicle fusion and exocytosis.

Indication: Levetiracetam is effective as adjunctive therapy in pediatric patients with focal onset seizures and in primary generalized tonic-clonic seizures [14]. Intravenous preparation has recently shown efficacy in neonatal seizures and status epilepticus [15, 16].

Adverse effect: There are reports of aggression, emotional lability, and oppositional behaviors, especially in pediatric group.

Dosage: Start with 5-10 mg/kg/day, titrated in steps of 5-10 mg/kg/week to usual maintenance dose of 20-40 mg/kg/day.

Zonisamide

Zonisamide has multimodal mechanism of action via inhibition of sodium channels, blockade of T-type calcium channels, and possibly inhibition of glutamate release. It strikes as being an effective AEDs with extensive clinical use in Japan [17].

Indication: It is efficacious in focal seizures with or without generalized tonic clonic seizures (GTCSs), primarily and secondarily generalized seizures including epileptic spasms of West syndrome, and other epileptic encephalopathies such as LGS [18-20].

Adverse effect: Sedation, fatigue and dizziness are common adverse effect. Rare adverse effects similar to topiramate may show nephrolithiasis, oligohidrosis and anhidrosis often marked by hyperthermia.

Dosage: The usual starting dose is 1-2 mg/kg/day for the first week, and the usual maintenance dose is 4–8 mg/kg/day.

Rufinamide

Rufinamide suppressed neuronal excitability by prolonging the inactive state of sodium channels, resulting in a decrease of frequency of sustained repetitive firing.

Indication: Adjunctive treatment of seizures associated with LGS in children older than four [21, 22]. Clinical trials have indicated that rufinamide can be also effective as adjunctive therapy in children and adolescents with drug-resistant focal seizures [23].

Adverse effect: Somnolence, nausea and vomiting are commonly observed.

Dosage: It is usually started at 10 mg/kg/day, titrating up by 10 mg/kg/day every 2 days to a target dosage of 45 mg/kg/day.

Lacosamide

Lacosamide is a functionalized amino acid that selectively augments slow inactivation of sodium channels, thus stabilizing of neuronal membranes and inhibiting of sustained repetitive neuronal firing.

Indication: The efficacy of adjunctive treatment in adult with refractory epilepsy was established [24]. But there are sparse data on children, only some retrospective data with small number of patients attainable. It showed 30-50% of efficacy rate in children with refractory epilepsy [25, 26].

Adverse effect: Adverse effects in children were similar to those seen in adults, with dizziness, headache, and nausea [27]. Concomitant use of another sodium-channel blocking AEDs increased the likelihood of treatment failure [28].

Dosage: A starting dose of 1 mg/kg/day may be considered for initiation of therapy. Doses should be titrated at weekly intervals, and the effective doses have ranged from 4 to 12 mg/kg/day.

Perampanel

Perampanel selectively inhibits α-amino-3-hydroxy 5-methyl-4-isoxazolepropionic acid (AMPA)-induced calcium influx, thus reducing neuronal excitation.

Efficacy: The pooled data from the three phase III studies showed improved seizure control in perampanel-treated adolescent, consistent with the overall findings in adults [29, 30].

Adverse effect: Dizziness, somnolence, and headache are frequently observed.

Dosage: Perampanel should be initiated at a dose of 2 mg/day, taken at night, and titrated by increments of 2 mg every 2–4 weeks according to the clinical need to achieve the maximum tolerated dose (up to 12 mg/day).

Diet therapy

Fasting as a treatment for epilepsy was mentioned in the New Testament of the Bible, and the first scientific approach began in 1921 by Dr. Rawle Geyelin reporting the outcomes of several epilepsy children who benefited from fasting at the annual meeting of the American Medical Association [31]. In the following decades after introduction of AEDs in the 1940s and 1950s, fasting and the use of the ketogenic diet (KD) fell out of favor. Later it has been reemerged in the last two decades as a valuable option among alternative treatment of drug resistant epilepsy, mainly in children [32]. It is now available over 50 different countries, and because of publication with large data collection, major concerns regarding its side effects, difficult compliance and doubts on efficacy have been overcome [33, 34].

The classic KD is composed of 3:1 to 4:1 ratio of fat to protein plus carbohydrates (both in grams). In this formulation, fat is the major calorie source, thus only daily amount of protein is required with severely restricted carbohydrates. Additionally, modernization of the KD has led to two other less restricted versions of diet therapies: the modified Atkins diet (MAD) and low-glycemic index treatment (LGIT). The MAD is 'modified' from the Atkins diet, which allows intake of protein and fat but strictly restrict carbohydrates, created to combat obesity [35]. The glycemic index (GI) is a measurement of carbohydrates effecting on blood glucose levels. The LGIT allows more liberal total carbohydrate intake, but that are restricted to foods that produce little increase in blood glucose (GI <50) [36]. These two diet therapies may be beneficial for adults and patients in developing counties in which strict supervision is unavailable, compared to classic KD.

Although, KD is treatment of choice in cases with certain types of epilepsy (e.g., glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase deficiency), it is a broad spectrum treatment that can be used safely and effectively for most types of seizures and epilepsy syndrome [34, 37, 38].

A randomized, controlled trial of 145 children showed that 38% (28 out of 73) of ketogenic diet group had greater than 50% seizure reduction compared to 6% (4 out of 72) of control group ($p<0.001$) [33]. The MAD also showed comparable results in a review of pooled data from 32 studies; 48% had > 50% seizure reduction and 13% were seizure free [39]. A recent randomized comparative investigation was performed in 104 children with intractable epilepsy treated with MAD versus classic KD. As a result from the study, MAD may be considered as the primary choice for the treatment of intractable epilepsy in children over KD, but the classic KD recommended as the first line of diet therapy in patients younger than two years of age [40].

The mechanism underlying its clinical efficacy remains unknown. It is suggested that KD affects intermediary metabolism that influences the dynamics of the major inhibitory and excitatory neurotransmitter systems in brain, increases level of ATP through enhanced mitochondrial respiration and provides the neuroprotective effect [41, 42].

Adverse effect: Long term adverse effects of the ketogenic diet include growth retardation, gastrointestinal symptoms, carnitine deficiency, kidney stones, and elevated lipids. However, these complications are manageable with various conservative treatments [43]. We recommend 5- to 7- day hospitalization for close monitoring of potential side effects when initiating ketogenic diet as well as adequate education for family for its safe and exact home maintenance [44].

There are treatment gap for intractable epilepsy, accessing newer AEDs and surgical treatment, and these limitations can be seen particularly in developing countries. Thus, diet therapies mentioned above are recommended to treat patients in all cultures for its easy accessibility and cost effectiveness.

Epilepsy surgery

The surgical treatment has become increasingly more valuable and it is now accepted for the management of drug resistant focal epilepsy due to major advances in presurgical investigation methods, and surgical techniques. Thus, the outcome from current surgical methods has improved for the last two decades and furthermore, recent research emphasis that surgical treatment should not be viewed as a last resort [45].

Epilepsy surgery for children is not simply an extension of adult procedures because additional complicating factors such as different causes of epilepsy, surgical techniques other than temporal lobe resection, consideration of timing of surgery and its risk must be recognized. Hippocampal sclerosis is the

most common surgical candidate in adult, which is uncommon in children. The three leading etiologies in children are cortical dysplasia (42%), tumors (19%), and stroke or atrophic lesions (10%) [46]. And these age-related differences in etiology result in variety spectrum of surgical procedures, which are commonly multilobar or functional hemispherectomy, and temporal lobe resections only account 23% [46]. One growing concept is that successful epilepsy surgery can be achieved in cases with wide spread electroencephalography (EEG) or MRI abnormalities, and this concept was best shown in early onset epileptic encephalopathies in children [47- 49]. In pediatric group, the benefits of epilepsy surgery are not only limited to reduction of seizure frequency, but also preventing the disabling psychosocial consequences and intellectual disability during critical period of development [49].

The assessment to identify an epileptogenic zone include a study of seizure semiology, neurological exam, video EEG monitoring, high resolution MRI and neuropsychological evaluation. Other helpful advanced neuroimaging include 18 F-FDG-positron emission tomography (PET), ictal and interictal single photon emission computerized tomography (SPECT) and magnetoencephalography (MEG).

Seizure freedom is achieved in a variable proportion of patients according to epilepsy type, underlying pathology, duration of follow-up, and series reported. A comprehensive review of surgical outcome conducted in 2008 showed that overall freedom of seizure in 59-70% of children (60-91% for temporal and 54-66% for extratemporal resections) [50].

Surgery can be one of two types. Curative aims at suppression of the epileptogenic focus through a resective and disconnective surgical procedure and palliative is to minimize the frequency and severity of seizures (corpus callosotomy and multiple subpial transections). Curative surgery procedures consists of focal cortisectomy and lobal resection depending on its location (temporal or extratemporal resection), and functional hemispherectomy (anatomically subtotal but physiologically completely disconnective procedure). Corpus callosotomy was first used in 1939 to stop bilateral synchrony of cortical epileptiform activity and rapid bilateral motor manifestations. This procedure is mostly performed in patients with LGS to reduce the number of disabling drop attacks.

Vagus nerve stimulation, which is one of the neuromodulatory treatment can be considered. It functions as a multi-programmable pulse generator that is implanted in the patient's upper chest and delivers electrical current to the vagus nerve. Although this device has been approved as an adjunctive treatment for patients over 12 years of age with intractable focal-onset epilepsy, it is often used in younger children and in patients with generalized epilepsy [51].

In conclusion, Intractable epilepsy in children should be more actively treated by newly developed AEDs, dietary treatment, and surgery to provide better outcome in seizure, development and behaviors.

Conflict of Interest

The authors state no conflict of interest.

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