

INTRACTABLE EPILEPSY IN CHILDREN

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Abstract

Objective

Epilepsy is a common disorder affecting approximately 1% of the population. It is estimated that about 20-30% of the patients become refractory to proper medical therapies. Such cases are often termed intractable. Intractable epilepsy (IE) is a serious condition in children, leading to significant impairment in quality of life, as well as behavioral and psychiatric problems.

In this review, we tried to define intractability, mention the causes of intractable epilepsy and its predictive factors in children, and outline the management and various treatments of intractable epilepsy.

Keywords: Intractable Epilepsy, Management, Children.

Introduction

Epilepsy is a chronic neurologic condition characterized by recurrent, unprovoked seizures requiring continuous medication for long-term management (1). Epilepsy is a common disorder affecting approximately 1% of the population. It is estimated about 20-30% of patients become refractory to medical therapy (2), (3), (4), (5), (6). Such cases are often termed intractable. Intractability, however, is not evenly distributed among patients with epilepsy. It is more common in those with mental retardation, neurological deficits, or both, and generally in patients with detectable structural brain damage (7).

Intractability includes all patients who do not achieve complete control of (disabling) seizures (8). Medical intractable epilepsy is therefore usually defined as continued seizures in children despite adequate therapy with three or more Anti Epileptic Drugs (AEDs), used alone, serially, or in combinations (3), (9).

Intractable Epilepsy (IE) is a serious condition in children, leading to significant impairment in the Quality of Life (QOL), as well as behavioral and psychiatric problems including depression, sleep disorders, mood disorders, cognitive delay and poor scholastic performance. Most patients become severely emotionally affected, and coping with this chronic handicap may pose a burden on the family as well as on social, educational, and health services (10), (11). In addition, numerous medical problems, some of which are potentially life-threatening, arise as a result of uncontrolled seizures including aspiration, cardiac arrhythmias, electrolyte imbalances, brain edema, renal failure, unexplained sudden death, and refractory status epilepticus (12). Besides, these children are more prone to drug toxicity and drug interactions resulting from polypharmacy and are at higher risk of developing behavioral and academic difficulties (13).

It is best to refer cases of intractable epilepsy early to a tertiary center for appropriate evaluation as well as to get guidance on management options like newer AEDs, the ketogenic diet and surgery.

Causes of intractable epilepsy

Intractability here is taken to mean epilepsy that is not controlled after an adequate trial of first line conventional anti epileptic drugs, singly or in combination. It is not the frequency of seizures as such that defines them as intractable, but rather their resistance to be controlled by treatment. When confronted with a child with apparently intractable epilepsy, three questions need to be considered:

- (1) Does the patient have epilepsy?
- (2) What is the underlying cause/diagnosis?
- (3) Is the epilepsy truly intractable?

1) Does the patient have epilepsy?

It is estimated that 20 to 30% of the patients referred for the management of intractable epilepsy do not have epilepsy (14), (15), (16), (17).

There are a large number of common non-epileptic paroxysmal disorders in childhood and it behooves the clinician who deals with epilepsy to be familiar with them.

Complementary information is given by the electroencephalogram (EEG). Paroxysmal activities on the EEG do not mean that a patient's attacks are necessarily epileptic in nature. Video Monitoring of a seizure during EEG recording is extremely helpful. In cases with very frequent attacks, long term monitoring with a Video EEG and polygraphy may help resolve the issue.

2) What is the underlying cause/diagnosis?

In some cases the cause is obvious, such as asphyxial brain damage, a congenital infection, cerebral malformation, or a metabolic disorder.

One important, recently uncovered factor in the development of intractable epilepsy is the overexpression of a variety of drug resistance proteins or their genes in the brain tissue.

This overexpression has been observed in the brain tissues taken from areas of cortical dysphasia,

hippocampal sclerosis, and tubers from patients with refractory epilepsy (18).

Several proteins have been implicated to date, and all belong to the ATP-binding cassette superfamily that also has been associated with resistance of cancer cells to antineoplastic agents.

They are Multi Drug Resistance gene-1-P-Glycoprotein (MDR1), Multidrug Resistance-associated Proteins (MRP1& MRP2) and the Major Vault Protein (MVP). By contrast, control tissues have no or low expression of these four types of proteins (19, 20).

Because these multidrug transporters restrict the entry of lipophilic molecules, such as many of the antiepileptic drugs, into brain, their overexpression reduces effective drug concentration at target sites. It is not clear, however, whether overexpression of these proteins is the cause or the result of intractable seizures. In animal Models, recurrent seizures have been shown to induce the multidrug resistance gene, and antiepileptic drugs have been able to up-regulate MDR1 and some other multidrug transporters. From these data, is suggested that there could also be a genetic contribution to drug resistant epilepsy (18).

However, in many cases, this is not so and there is always the question whether there is an underlying neurodegenerative disease.

All cases of intractable epilepsy should have a high resolution computed tomography, and even better, magnetic resonance imaging of the brain, to detect brain structural defects.

Although there are a large number of neurometabolic diseases in which seizures are prominent, most of them will be suggested by other clinical features. There are, however, a few conditions in which intractable epilepsy may be the most prominent initial feature. Pyridoxine dependency should always be excluded, particularly in infantile epilepsy; because prompt diagnosis and treatment can stop and prevent these seizures and consequential developmental disabilities. (21), (22), (23).

It is important to classify the type of the seizures. The seizure type may provide a clue to the cause of the seizure disorder. Precise delineation of the seizure may allow a firm basis for making a prognosis and choosing the most appropriate treatment (24).

3) Is the epilepsy truly intractable?

When reviewing the history of previous treatments it is necessary to document the following for each antiepileptic drug: the duration of treatment, dose/kg, clinical effects, side effects, and blood concentrations. If a drug has been stopped after a very short time the reason for changing it needs to be determined. When such a drug history is available it should be clear whether there has been an adequate trial of each drug, alone or in combination. Given the spontaneously fluctuating nature of most types of epilepsy, each trial of drugs or combination should be given for a minimum of one month (unless there is a severe side effect or exacerbation of seizures). For this reason it is normally preferable that drug changes occur at home and be monitored in outpatient setting rather than in a hospital. This will prevent the physician from changing the drug in a few days after starting, in a hospitalized child with uncontrolled seizures. It is also important to decide whether an adequate dose of each drug has been administered. In this regard the concept of a “therapeutic range” of blood concentrations for antiepileptic drugs is not particularly helpful. Persistently low blood concentrations may indicate non-compliance, which is an important cause of “poor seizure control”. A drug history such as this may reveal that an insufficient trial of one or more drugs may have been given and in some patients, going back to an antiepileptic drug that has previously been tried in a different dose or combination is sufficient to control the seizures. The possibility that the treatment is making the epilepsy worse must always be considered. It is probable that all the commonly used antiepileptic drugs aggravate seizures at some time, for example (Carbamazepine/Oxcarbazine may worsen and sometimes even induce absence/myoclonic seizures (25), (26), Gabapentin may increase complex partial seizures in some patients (27)) and some drugs (penicillin, INH, theophylline, insulin, lithium, prednisolone, oral contraceptive pills, chloroquine etc.) can be epileptogenic (27).

Occasionally, seizures will improve on decreasing or stopping drugs (28); more often, however, the seizures remain the same, but alertness and coordination improve (29).

Predictive factors in intractable epilepsy

Accepted various predictive factors in IE (27), (30) are listed in table 1:

Table 1: Predictive factors in intractable epilepsy.

Seizure Type
1. Partial seizures
2. Multiple seizure types
3. High seizure frequency
4. Seizure onset in infancy
5. Febrile seizures.
6. Non idiopathic (non-inherited)
7. Specific Epilepsy Syndromes (e.g, West Syndrome, LennoxGastaut Syndrome)
8. Myoclonic seizures
9. Neonatal seizures
Clinical
1. Focal neurological deficit
2. Family history of epilepsy
3. Cerebral palsy
4. Mental retardation
5. Behavioural disorders
6. EEG abnormality
7. CT scan abnormalities
8. Sex (male)
Etiological
1. Organic brain lesions (e.g, mesial temporal lobe sclerosis, tuberous sclerosis, congenital cerebral anomalies etc.)
2. Head trauma
3. CNS infections
4. Hypoxic ischemic encephalopathies
5. Metabolic disturbances (phenylketonuria, maple syrup urine disease, mitochondrial encephalopathy).

Management

The general principles of managing intractable seizures are as follows (27):

- Review diagnosis and history of the epilepsy. The types of seizures and the epilepsy syndrome should be classified on the basis of clinical features and

the EEG. In addition, imaging of the brain with high quality MRI is appropriate, looking for an underlying structural lesion.

- Check serum concentrations of AEDs.
- Review past and present AED treatment.
- Select the AED that is most likely to be efficacious and with the fewest side effects.
- Adjust the dose of the selected drug to the optimum with increments made if seizures continue and side effects do not occur.
- Attempt to reduce and discontinue other AEDs, particularly those that have not aided seizure control and are suspected of giving rise to adverse effects.
- If seizures continue despite a maximal tolerated dose of a first line AED, another first line drug should then be commenced, and increased to an optimal dose.
- If combinations of two first line AEDs is unhelpful, the drug which appears to have the most effect and fewest side effects should be continued, and the other AED be replaced with a second-line drug.
- If the second line drug is ineffective, withdrawal of the initial agent should be considered.
- Considered using a novel AED. Because of the limited clinical experience with newer AEDs it appears appropriate to recommend these drugs for the patients with refractory seizures in whom other drugs are not effective or cause intolerable side effects.
- The above-mentioned scheme will generally take a number of months or even years to work through. If satisfactory control cannot be obtained with drugs, consider the possibility of surgical treatment of the epilepsy.

Other treatments:

Up to 70-80% of the patients with epilepsy can be seizure free with antiepileptic drugs (AEDs) (31), (32), and chronic epilepsy or medically refractory epilepsy is seen in about 20-30% of cases.

Options for the Management of Refractory Epilepsy

a. Second line drugs

- 1) IVIG treatment
- 2) Ketogenic diet

3) Prednisolone treatment

4) Herbal treatment

b. Surgery, Gama knife and neural stimulation (Vagus, DBS)

c. Seizure prediction and prevention

d. Gene therapy

e. Stem cell therapy

f. Pharmacogenetics

a) Second Line Drugs

The chances of the addition of a second-line drug resulting in a 50% reduction of seizures is 20-50%, however, the chances of the patient becoming seizure free is less than 10% (27), (33).

1) IVIG Treatment

Immunological mechanisms have been suspected in the pathogenesis of epileptic seizures in some patients and in experimental animal models of epilepsy. The effects of globulin treatment in epilepsy were first studied by Pechadre et al. in 1977 (34). They observed the disappearance of seizures and EEG improvement in epileptic children treated with intramuscular immunoglobulin for allergic seasonal diseases. Since the initial report, IVIG has been employed in intractable epilepsy, West and Lennox-Gastaut Syndromes (LGS) (35).

There is no dose protocol for IVIG treatment. In the literature, every study has a different dose schedules and the total dose of IVIG varies between 0.3 and 6.8 g/kg for a period of 0.15 to 12 months. The mean seizure reduction reported by authors ranges from 0% to 90% (35), (36).

2) Ketogenic Diet

The Ketogenic Diet (KD) has been used worldwide for the treatment of intractable childhood epilepsy (37), (38). However, the KD is not yet a convenient therapy, especially in older children and adolescents (39), (40). The Atkins diet induces a state of ketosis by providing a high fat content and few carbohydrates and it is suggested that this diet may control seizures through a mechanism similar to the KD (41).

3) Prednisolone Treatment:

Steroids, including prednisolone and adrenocorticotrophic hormone (ACTH), have been used in the treatment of epilepsy for over 68 years (42), (43) and are recognized as relatively safe and effective for infantile spasms (44). However, studies of the use of steroids in the treatment of epileptic conditions other than infantile spasms are limited (45).

Some studies have showed that after prednisolone treatment in cryptogenic epileptic encephalopathies other than infantile spasms, about 25% to 59% of the children become seizure free and 11% to 40% show reductions in seizure frequency (45), (46), (47).

4) Herbal and Supplemental Treatments:

There are two documented herbal treatments for intractable epilepsies in Iran as follows:

1) A double-blind study found that using the extract of the black seeds of the *Nigella Sativa* plant helped control seizures in children (48).

2) In a double-blind clinical trial, conducted as a pilot study, researchers concluded that the essential oil of *Rosa Damascena* had beneficial antiepileptic effect in children with refractory seizures (49).

In a study, administration of high dose oral pyridoxine as a therapeutic adjunct to routine AEDs for the treatment of recurrent intractable seizures was useful (50). Serum Selenium concentration was lower in patients with intractable epilepsies compared with the control group, in a case-control study (51). Results are inconsistent regarding whether the use of fish oil can decrease seizure frequency in people with epilepsy (52). Several studies by a single research group hint that supplement Melatonin may improve the quality of life in children with epilepsy (53). People with epilepsy should seek medical supervision before using any herbs or supplements.

b) Surgery

Once the newer antiepileptic drugs have failed, the choice of treatment is surgical ablation of the epileptogenic area. The goal of epilepsy surgery is to identify the abnormal area of cortex from which the seizures originate and remove it without causing any significant functional impairments (54). Prior to

surgery, the presurgical evaluation, which involves the collaboration of neurologists, electrophysiologists, neuropsychiatrists, neurosurgeons, and nurses, is used to determine if a patient has seizures that are appropriate for surgical management and, if so, the type of surgery most likely to succeed (55,56).

The primary components of the presurgical evaluation include a detailed clinical history and physical examination, advanced neuro-imaging, Video-EEG monitoring, neuropsychological testing and assessment of psychosocial functioning.

Major questions to be answered with this evaluation are:

- 1) Are the seizures focal or generalized?
- 2) If focal, are they temporal or extratemporal in origin?
- 3) Is there a lesion associated with the seizures?
- 4) If surgery is undertaken what functional deficits, if any should be anticipated?

Types of surgical approaches are discussed in another review (54).

c) Seizure Prediction and Prevention

What if there is no surgically remediable lesion and the patient continues to have frequent seizures? Seizures occurring without warning are the most disabling aspect. On demand release of short acting drug or electrical stimulation during the preictal state would prevent seizure (57). Trials are being conducted for early seizure detection through implanted intracranial electrodes and prevention of the seizure by responsive electrical stimulation (58), (59). Initial reports have shown reduction of seizures by 50% or more in over 40% of refractory epilepsy patients (60).

d) Gene Therapy

The goal of gene therapy in epilepsy is for sustained anticonvulsant, and antiepileptogenic effect, and to block the progression of the disease. The GABAergic system is the first target for gene therapy to increase GABA levels in the epileptogenic area. Implantation of genetically engineered inhibitory cells into the focus may become an option (61).

e) Stem Cell Therapy

Some authors review cell transplantation as an alternative approach to the treatment of epilepsy. Recent work in animal models shows that grafted neuronal precursors that differentiate into inhibitory interneuron can increase the level of local inhibition. Grafts of these inhibitory neurons could help restore equilibrium in temporal lobe epilepsy (62). Neuronal precursor cells derived from embryonic stem cells functionally integrate into the host brain tissue after transplantation (63).

f) Pharmacogenetics

Some patients simply do not respond to AEDs right from the start and there are some other patients who are severely allergic to some AEDs, while the majority can tolerate them. This difference in response or sensitivity is partially due to genetic variations. The ultimate goal of pharmacogenetics is to use the genetic make up of individuals, to predict drug response and efficacy, and to predict potential adverse drug reactions (64). So far, the emphasis is on the control of seizures, i.e. antiepileptic, which is now shifted to prevention of epilepsy, i.e. antiepileptogenic which also means a cure, not just symptom control (65).

In conclusion, we believe that diagnosis of intractable epilepsy should be firmly ascertained in the first place. Conditions which mimic epilepsy such as: breath holding spells, faint, sleep disorders, movement disorder, etc,... should be ruled out. Those cases whose seizures recurrence are due to inadequate drug dosage or secondary to using inappropriate drug for the seizure type which affects the patient, should be recognized. Upon reaching the diagnosis of refractory epilepsy, the best way of management of any individual child should be delineated.

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