



Intractable Epilepsy in Children

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ABSTRACT

A seizure is defined as a paroxysmal and transient occurrence of signs or symptoms resulting from abnormal synchronous or excessive neuronal activity in the brain. About 15 to 40 percent of children who have any type of seizure are resistant to standard anti-seizure drugs, so called intractable epilepsy. Before documenting the seizure attacks as refractory, the selected drugs using for the type of seizure and dose of them should be checked. There are several factors that predict development of refractory seizures. These include age <1 year, multiple seizures before starting the treatment, myoclonic seizures, neurologic defects, neonatal and daily seizures, male gender, and first abnormal electroencephalogram and brain imaging (including computerized tomography scan and / or MRI). Options for the management of refractory epilepsy, after prescribing routine anti-seizure drugs are: Second line drugs (IVIG treatment, Ketogenic diet, Prednisolone treatment or Herbal treatment), Surgery and Stem cell therapy. Because none of these methods can stop all the drug-resistant epilepsies, researches are going on. .

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Introduction

Seizure is defined as a paroxysmal and transient occurrence of signs or symptoms resulting from abnormal neuronal activity originated in the brain. Seizure disorder is used to name any one of several disorders, like febrile seizure, epilepsy, unprovoked seizures and symptomatic seizures secondary to infectious, metabolic, or other etiologies (e.g., hypocalcaemia, hematoma, meningitis, etc.) (1).

Epilepsy is a common disorder of the brain that is characterized by an enduring predisposition to generate unprovoked seizures (2). Seizure is the most common form of neurologic disorder in children. Single seizure is happened in 4 to 10 percent of children with age younger than 16 years (3). About 15 to 40 percent of children who

have any type of seizures are resistant to standard anti-seizure drugs (4-6). These children have an increased risk of mortality rate, estimated at 1.37 per 100 person-years (7); whereas whom become free of seizure have no increased risk of mortality in comparison with normal children (8).

The International League Against Epilepsy (ILAE) proposed a definition of drug-resistant epilepsy as a failure of controlling seizures with use of at least 2 tolerated and appropriately chosen anti-seizure drugs (9). Intractability is more common in those with neurological deficits, mental retardation, and generally in patients with detectable structural brain damage (10). Intractable Epilepsy (IE) in children, can lead to significant impairment in the Quality of Life (QOL), as well

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as psychiatric problems including sleep or mood disorders, depression, cognitive delay and poor scholastic performance (10). Most affected children will have emotional disorders, and will have additional charge on the family as well as educational, social, and health services (11,12). Besides, due to drug interactions resulting from polytherapy, these patients are at risk of drug toxicity and behavioral and academic difficulties (13).

It is best to early refer cases of refractory seizures to a tertiary center for appropriate management as well as to earn guidance on different treatments, like newer anti-seizure drugs, the ketogenic diet or surgery.

Literature Review

Diagnosis

At first, one must differentiate epilepsy from other seizure-like (non-epileptic) events based on a detailed history of the attack. About 25-30% of the patients referred for refractory epilepsy have psychogenic non-epileptic seizures (PNES) (14). Besides, the physician must rule out other non-epileptic paroxysms, like breath-holding spells, migraine, syncope, movement and posture disorders, and sleep disorders (narcolepsy or cataplexy). The physician may need to use long term monitoring to rule out non-epileptic paroxysms. Toxicity and also metabolic disorders like hypoglycemia, hypocalcaemia, hypomagnesaemia, hyponatremia and also hypernatremia can cause seizures, resistant to anti-seizure drugs.

Pyridoxine dependency should always be excluded, particularly in infantile epilepsy; because prompt diagnosis and treatment may stop these seizures and prevent consequential developmental disabilities (15).

Before documenting the seizure attacks as refractory, the selected drugs using for the type of seizure and also the dose of drugs should be checked. 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 (alone or in combination) should be given for at least 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 the hospital. This will prevent the physician from changing the drugs in a few days after starting, in a hospitalized child with uncontrolled seizures (10).

The possibility that the treatment is making

the epilepsy worse must always be considered. It is probable that all the commonly used antiepileptic drugs may worsen seizures at some time, for example carbamazepine has been reported to precipitate or worsen some types of seizures, including absence, atonic, or myoclonic seizures in patients with generalized epilepsies in which their EEGs show bursts of diffuse and bilaterally synchronous spike-and-wave activities (16-18). Phenytoin and vigabatrin on the other hand, can aggravate some type of seizures, particularly generalized seizures, whereas gabapentin has been reported to precipitate myoclonic jerks (18). There are many reports showing an increased risk of symptomatic seizures especially with the use of unsubstituted penicillins, fourth-generation cephalosporins, ciprofloxacin, and imipenem in patients with renal dysfunction, epilepsy, or brain lesions (19).

Management

The general principles of managing intractable seizures are as follows (10):

- Review history and diagnosis of the epilepsy. The seizures type and if possible, the epilepsy syndromes should be classified on the basis of history, clinical features, and the EEG. In addition, for detection of underlying structural abnormalities, high quality brain MRI is appropriate.
- Check serum concentrations of anti-seizure drugs.
- Review past and present anti-seizure treatment.
- Select the anti-seizure drug that is most likely effective and has the fewest side effects.
- Increase the dose of the selected drug if seizures continue without side effects.
- Attempt to reduce and discontinue other anti-seizure drugs, particularly those that did not reduce seizures or are suspected of giving rise to adverse effects.
- If seizures continue despite a maximum tolerated dose of a first line anti-seizure drug, another first line drug should be prescribed, and increased to an optimal dose.
- If combinations of two first line anti-seizure drug are not helpful, the drug which has more effectiveness and fewer side effects should be continued, and the other anti-seizure drug be replaced with a second-line drug.
- If the second line drug is ineffective, withdrawal of the initial treatment should be considered.
- Consider using a novel anti-seizure drug. Because of the limited clinical experience with newer anti-seizure drugs it may be better to recommend them for children with refractory seizures in whom other drugs caused intolerable side effects or were not effective.

• If seizures are not controlled satisfactorily with drugs, consider the possibility of surgical therapy. Other treatments: Up to 70-80% of the patients with epilepsy can be seizure free with anti-seizure drugs (20), and medically refractory epilepsies are in about 15-40% of patients.

Options for the management of refractory epilepsy, after prescribing routine anti-seizure drugs:

- a. Second line drugs
 - 1) IVIG treatment
 - 2) Ketogenic diet
 - 3) Prednisolone treatment
 - 4) Herbal treatment
- b. Surgery
- c. Seizure prediction
- d. Stem cell therapy

a) Second Line Drugs

On adding a second-line drug, the chance of a 50% reduction in seizures is estimated 20-50%, however, the patient has less than 10% chance to be seizure free (21).

1) IVIG Treatment

Immunological mechanisms have been suspected in the pathogenesis of epileptic seizures in experimental animal models of epilepsy and even in some epileptic patients. For the first time, Pechadre et al. in 1977 studied the effects of globulin treatment in the treatment of epilepsy (22). They observed that in epileptic children treated with intramuscular immunoglobulin for allergic seasonal diseases, seizures were controlled and the EEG improved.

Some new findings suggest that intravenous immunoglobulin has potentially high efficacy in the treatment of children with refractory epilepsies with low side effects. Intravenous immunoglobulin could reduce multiple types of seizures due to various epilepsy etiologies, including those of unknown cause (23,24).

2) Ketogenic Diet

The Ketogenic Diet (KD) has been used for the treatment of intractable epilepsy in children (25). However, the KD cannot be simply tolerated especially in older children and adolescents so is not a convenient therapy. The Atkins diet has a better tolerance and induces a state of ketosis by providing a high fat content with only few carbohydrates and may control seizures as well as the KD (25).

3) Prednisolone treatment

For several years, steroids like prednisolone and methylprednisolone and also adrenocorticotrophic hormone (ACTH) have been used to treat infantile spasms. However, only a few studies

are focused on the use of steroids in the treatment of epilepsies beyond the infantile spasms (26).

4) Herbal treatment

Different Herbal medications including Thymoquinone, Nigella Sativa, Rosa Damascena, Citrus aurantium L, Chaihu-longu-mulitang, and Zhenxianling have been recommended due to their anti-seizure effects (3,6,27,28). If specific herbal medication is used with suggested dosage, it may have less side effects and be more acceptable for general population.

b. Surgery

In infants and children, epilepsy surgery has become an accepted treatment for drug resistant epilepsies. Certain epilepsy syndromes that are surgically treatable have been delineated and especially if cognitive or behavioral development is being compromised, should be offered earlier. Advances in neuroimaging (especially MRI), has helped identifying better surgical candidates. Pre-surgical evaluation includes clinical assessment, structural and functional imaging, inter-ictal EEG, simultaneous video -EEG, with analysis of seizure semiology and ictal EEG and other optional studies like neuropsychology. If data for resecting a lesion are matched, resective surgery is offered, with preservation of eloquent cortical areas subserving motor, language and visual functions. When data are not matched or when the MRI doesn't show any lesion, invasive (direct cortical) EEG maybe useful. In generalized or multi-focal seizures, palliative surgeries like corpus callosotomy and vagal nerve stimulation are probably useful. In about 67% of patients undergoing resective surgery, a good outcome is seen with a low mortality and / or morbidity (29).

c. Seizure prediction

There are several factors that predict development of refractory seizures. These include age <1 year, multiple seizures before starting the treatment, myoclonic seizures, neurologic defects, neonatal and daily seizures, male gender, and first abnormal EEG and brain imaging (including computerized tomography scan and / or MRI) (30).

e. Stem cell therapy

Existing anti-seizure drugs are not efficient in some patients; that necessitate finding alternative approaches such as stem cell therapy.

Stem cell-based therapy may be an effective strategy to repair various pediatric neurological disorders. Current therapeutic methods for children with neurological disabilities are limited, although various researches on animal models have

shown effectiveness of the cell therapy (31).

Some researchers reported the use of autologous patient-derived mesenchymal stem cells (MSC) for treatment of symptomatic refractory epilepsies in a Phase I open label clinical trial. Injections of MSC were well tolerated and did not cause any severe adverse effects. Three out of 10 patients in MSC therapy group after 1 year follow up, achieved remission, and additionally half of patients (5 out of 10) became responders to anti-seizure drugs, whereas in control group, only 2 out of 12 patients became responders (32).

Conclusion

Epilepsy is a common neurologic disorder in childhood and about 15 to 40% of children with seizures are resistant to standard anti-seizure drugs. Because drug-resistant epilepsies can worsen life style of child and the family, true diagnosis and managements are necessary. The initial diagnosis is based on a detailed seizure history to differentiate epilepsy from other seizure-like (non-epileptic) events. There are many approaches to control these seizures including: standard anti-seizure drugs, second line drugs (like: IVIG treatment, Ketogenic diet, prednisolone treatment, herbal treatment), surgery and stem-cell therapy. Because none of these methods can stop all the drug-resistant epilepsies, more researches are needed.

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Conflict of Interest

The authors declare no conflict of interest.

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