ABSTRACT

Epilepsy is a common neurological disorder in childhood. In a majority, the cause of epilepsy remains a mystery in spite of extensive investigations. The aim of drug treatment is to effectively stop the seizures with minimum of side effects, causing no impairment of long term learning abilities of the child. Up to 30% of children with epilepsy may continue to have seizures in spite of adequate drug therapy. In this review, an overview of the recent advances that affect the diagnosis, prognosis and therapy of childhood epilepsy including the dilemmas of everyday practice is presented.

Keywords: epilepsy, genetics, antiepileptic drugs, teratogenicity.
INTRODUCTION

A seizure or convulsion is a paroxysmal, time-limited change in the motor activity and/or behavior that results from abnormal electrical activity in the brain. Seizures are the most common pediatric neurologic disorder, with 4% to 10% of children suffering at least one seizure in the first 16 years of life. The incidence is highest in children younger than 3 years of age, with a decreasing frequency in older children. Epidemiologic studies reveal that approximately 150,000 children will sustain a first-time, unprovoked seizure each year, and of those, 30,000 will develop epilepsy.¹ A majority of these seizures are provoked by fever (in the age group of 3 months to 6 years), infections, trauma or hypoxia. Epilepsy is the term used to describe recurrent unprovoked seizures that do not include the seizures provoked by the above events. A majority of children with epilepsy respond well to therapy but it is estimated that up to 30% become refractory to medical treatment.²

In this article, some recent advances that influence the drug therapy and prognosis of childhood epilepsy will be reviewed.

THE ROLE OF GENETICS IN THE TREATMENT OF EPILEPSY

Epilepsy and epilepsy syndromes are broadly divided into idiopathic and symptomatic epilepsies. Idiopathic epilepsies occur in the absence of any demonstrable brain lesions or neurological deficits or intellectual disabilities; genetic factors are strongly implicated in the causation of seizures in this group. In symptomatic epilepsies there is evidence of a brain lesion in the form of congenital anomaly/cortical dysplasia or a lesion secondary to vascular or traumatic events. The distinction between idiopathic (genetic) and symptomatic (acquired)
epilepsy is becoming increasingly blurred, particularly in cases without a demonstrable lesion; rather, the causation of epilepsies, ranging from genetic to acquired can be regarded as a biological continuum with ion channel dysfunction potentially providing the biological link.\(^3\)

The fact that some epilepsies tend to run in families has been known since antiquity and possibly this has contributed to stigmatization and occasional isolation of people with epilepsy. However, the importance of genetics in causation of epilepsy is being increasingly recognized since the last decade. Clinical and molecular genetics have revolutionized our knowledge in this field. Epilepsy is, essentially, a heterogeneous condition in which many causative factors may play a role. Genetically determined epilepsies are usually divided into two subgroups: those resulting directly from a functional consequence of a defective or mutated gene product or those due to structural brain abnormalities which are, in turn, caused by gene defects.\(^4\) One of the first epilepsy genes identified was that of nocturnal frontal lobe epilepsy gene, which is autosomal dominant and was mapped to chromosome 20q. It has been increasingly realized that gene mutations are directly or indirectly (along with the environmental factors) responsible for a number of children with intractable epilepsies. Examples are Dravet’s syndrome, myoclonic astatic epilepsy, neonatal convulsions, absence epilepsy, the syndrome of GEFS+ (generalized epilepsy with febrile seizures plus) and a newly identified phenotype of severe infantile multifocal epilepsy. It has become clear that genetic factors can strongly influence epileptogenesis and subsequent response to drug therapy in a considerable number of children with idiopathic epilepsy. In these conditions as well as in children with chromosomal abnormality syndromes with secondary epilepsy, genetic counseling plays an important role in the therapy.
THE ROLE OF FEBRILE SEIZURES IN HIPPOCAMPAL SCLEROSIS (HS) AND INTRACTABLE EPILEPSY

It has been known for some time that a significant number of children and young adults with intractable epilepsy have hippocampal/mesial temporal sclerosis. In adults with temporal lobe epilepsy, HS is the most common lesion found preoperatively with MRI and at temporal lobectomy. In our own study of a cohort of 30 children with temporal lobe epilepsy (TLE), 23.3% of children had HS. Over the last 10 years, evidence has accumulated showing a possible correlation between prolonged febrile seizures (febrile status epilepticus, FSE) and HS. Researchers have been debating whether children with a primary hippocampal malformation tend to develop FSE and subsequent intractable temporal lobe epilepsy or the prolonged seizures are the cause of hippocampal damage. Preliminary findings from FEBSTAT study, an ongoing multicentre study of FSE, designed to determine whether prolonged febrile seizures cause acute hippocampal damage, and if so, whether it leads to mesial temporal sclerosis show that hippocampal malrotation was observed in 12 out of 58 cases studied, all involving the left hippocampus. This raises the possibility that children with a malrotation of left hippocampus are more prone for prolonged febrile seizures and this somehow results in further damage to the hippocampus resulting in intractable temporal lobe epilepsy. If this is the case, further studies will probably involve long term anti-epileptic drug therapy (AED) administered to such children after the FSE and possible prevention of such damage.

OLD VERSUS NEW ANTI-EPILEPTIC DRUGS (AEDS)

There has been a considerable decline in the use of phenytoin and phenobarbital, the so-called first generation AEDs, in the long term treatment of childhood epilepsy. This is partly due to the troublesome and chronic, and at times alarming side effects
of these drugs but also because of availability of sodium valproate and carbamazepine and the newer AEDs which produce less alarming long term side effects. The ‘classic’ AEDs include sodium valproate and carbamazepine; both were introduced prior to the mid-seventies. Since 1993, a number of AEDs have been made available for epilepsy therapy; these are called ‘newer’ AEDs. The list includes lamotrigine, topiramate, vigabatrin, felbamate, levetiracetam, gabapentin and oxcarbazepine. Some of these drugs are often better tolerated than the classic drugs; in addition, drugs such as lamotrigine have a much broader spectrum of action compared to phenobarbital, phenytoin or carbamazepine. On the other hand, the long term safety profile of the ‘newer’ AEDs has not yet been established. Felbamate was hailed as an effective and safe AED when it was introduced in the early 1990s but subsequent identification of life threatening aplastic anemia and hepatotoxicity was a lesson to the neurologist that the long term side effects of newer AEDs can become obvious only after many years of use. Vigabatrin became popular since it was shown to be effective in infantile spasms, which is considered as one of the most refractory epilepsies in children. Nearly 16 years after the introduction of the drug, it was realized that therapy with the drug resulted in progressive and irreversible constriction of visual fields resulting in blindness in 20 to 40% of patients. Assessment of visual fields is not easy in young children and hence, the progressive visual loss is undetectable in such patients until a late stage. Therefore, caution needs to be exercised prior to use of the newer AEDs as first line drugs in children.

The drug therapy in epilepsy is started once the diagnosis is established. Treatment is generally started after 2 unprovoked seizures since the chances of recurrence are much higher after 2 or more episodes. Therapy can still be deferred if the seizures are considered infrequent, or if a benign epilepsy syndrome is suspected (eg, benign childhood epilepsy with centrotemporal spikes or benign rolandic epilepsy). On the other hand,
occasionally therapy is started after the very first seizure; this is done if the first seizure was a status or was complicated by a particularly complex electroencephalographic pattern (eg: epileptic encephalopathy) or a fairly severe brain malformation on brain imaging.8

It has been mentioned earlier that epilepsy in children can be broadly divided into 2 groups: idiopathic and symptomatic. There is a sub-group of children in whom a definitive cause is strongly suspected but not yet identified. This sub-group is currently called probably symptomatic (previously called as cryptogenic) group. The children who are in the symptomatic and probably symptomatic groups are more likely to have comorbidities such as developmental delay, hyperactivity and/or neurological deficits and are more likely to have an organic pathology in the brain, that becomes obvious on brain imaging. It is not surprising that this group of children may not respond to monotherapy; some of them may even develop intractable epilepsy.

Monotherapy is the cornerstone of drug therapy in epilepsy. For over 2 decades, carbamazepine and sodium valproate have been used as the primary drugs for therapy in childhood epilepsy; sodium valproate is recommended as the first choice in generalized onset seizures and carbamazepine in focal/partial onset seizures. However, this is likely to change with the recent developments; firstly, there is no evidence that carbamazepine has any advantage over valproate for the treatment of focal onset seizures.8,9 The results of SANAD study show that lamotrigine is preferable to carbamazepine as the initial monotherapy for focal onset seizures both in adults and children because lamotrigine is better tolerated, can be cost effective and the quality of life tended to be better with drug.10 Secondly, in children with mixed seizures, where focal onset seizures co-exist with myoclonic or absence seizures, carbamazepine tends to aggravate the latter varieties of seizures.11 A recent boxed
warning from FDA that patients with Asian ancestry should be screened for the human leukocyte antigen (HLA) allele HLA-B*1502 before receiving carbamazepine therapy makes it difficult for the paediatricians to continue to use carbamazepine as the first drug in focal onset seizures. The reason for this warning is that patients with this allele are at increased risk for Stevens Johnson syndrome and toxic epidermal necrolysis, two potentially fatal side effects associated with the drug. HLA-B*1502 occurs almost exclusively in patients with Asian ancestry, and its incidence is highest (10% – 15%) in those individuals from parts of China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan. It is likely that most paediatricians will now use sodium valproate as the first line therapy in both focal and generalized onset seizures in view of the above dilemma. However, lamotrigine is an alternative when valproate can not be used either because of liver dysfunction or other side effects of the latter. The bottom line, as stated in International League Against Epilepsy (ILAE) guidelines, is that no randomized control trials support a particular AED as initial monotherapy for most children with epilepsy; only oxcarbazepine for children with focal onset seizures was supported by level A evidence of efficacy and effectiveness.

With the effective use of an appropriate AED in the correct dosage, it is estimated that 60 to 70% of children may respond well. An alternative drug would be useful in those children who fail to respond to a particular AED even when the serum levels have been within the therapeutic range. It is estimated that up to 30% of children with epilepsy come under the category of ‘intractable epilepsy’, which is defined as continued seizures in children despite adequate therapy with 3 or more AEDs, used alone, serially or in combinations. Medical treatment of these children can prove tricky since the use of polytherapy is associated with higher risk of side effects. Drug interaction and increased risk of toxicity is a rule rather than exception when using polytherapy. Clear cut evidence of the superiority of one
combination over another is not available but certain regimens are known to have additive and/or synergistic effects.\textsuperscript{8} For example, valproate and lamotrigine act synergistically in refractory absences and myoclonic seizures. However, when used in combination, valproate increases the serum levels of lamotrigine and therefore the latter has to be started in much smaller doses and the dose increase has to be done gradually to avoid the risk of Stevens Johnson syndrome and other potentially fatal side effects.

**AEDS AND TERATOGENICITY**

All AEDs are potentially teratogenic. Obviously, this does not mean that a pregnant woman with epilepsy should be denied medications. The risk to the mother and the fetus from seizures and the possibility of status epilepticus that can result from withdrawal of AED during pregnancy must be weighed against the potential for teratogenicity of the AED used. Recent studies and establishment of anti-epileptic drug-pregnancy registries in US, Australia and Europe have revealed the true incidence and spectrum of teratogenicity of AEDs. Reynolds et al studied a total of 16,905 births to mothers with epilepsy and presented their data in a recent meeting.\textsuperscript{14} The incidence of congenital malformations for women with epilepsy but not taking AEDs was 2.8%, for women on a single AED (monotherapy), 6.2%, and for women on polytherapy, 10.2%. Interestingly another study showed that the rate of congenital malformation was highest (11.7%) in mothers on polytherapy that includes sodium valproate and lamotrigine. The incidence of spina bifida was 0.2%, the incidence of cleft palate was 0.3%, that of urinary tract malformation was 0.5%, club foot 0.7%, and the incidence of cardiovascular malformation was 0.9%. A comparison of effects of various AEDs showed some surprising results. It was concluded that the in-utero exposure to sodium valproate was
more likely to impair cognitive development with lower Mental Developmental Index Scores than exposure to other commonly used AEDs.\textsuperscript{15,16}

Maternal valproate use has been strongly associated with neural tube defects; however, other anomalies have also been reported, such as craniofacial defects, cardiovascular malformations and anomalies involving various body systems (some fatal). According to the US Centers for Disease Control and Prevention, the estimated risk for spina bifida among infants born to mothers receiving valproate during the first trimester of pregnancy is 1\% to 2\% compared with 0.14\% to 0.2\% in the general population as estimated by the American College of Obstetricians and Gynecologists. The FDA advises that tests to detect neural tube and other defects should be considered as part of routine prenatal care in valproate-treated women. Because of its potential to decrease the risk for neural tube defects, dietary folic acid supplementation should be routinely recommended both prior to and during pregnancy. In 2006, there was another notification by FDA regarding possible teratogenicity of lamotrigine advising that fetal exposure to lamotrigine during the first trimester of pregnancy may be linked to an increased risk for cleft lip or palate in newborns.\textsuperscript{17}

The bottom line is that during pregnancy polytherapy with multiple AEDs is far more dangerous than monotherapy and there are some drugs which seem to be relatively safer than others. It is important to maintain a regional registry of pregnant women with epilepsy; it is in the interest of the obstetrician to be in touch with a neurologist and a paediatrician while treating a pregnant woman with epilepsy to form a strategy to bring down fetal and maternal mortality and morbidity rates due to epilepsy or the drugs used in the treatment.\textsuperscript{18}
CONCLUSIONS

Recent research in the field of epilepsy has resulted in some exciting new developments that help us to understand the complex mechanisms of seizure production in the brain and explains the possible causations that make certain children more prone to get seizures than the others. At the same time, the ever increasing number of drugs available to treat epilepsy makes it imperative for us to be aware of their efficacy and safety profile prior to their use on children and pregnant women with epilepsy.

Address for correspondence: Dept of Paediatrics, Faculty of Medicine Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia. e-mail: gururaj@salam.uitm.edu.my

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