Review Article

Epilepsy, Antiepileptic Drugs and Educational Problems

Vinayan K.P.

Epilepsy is a chronic disorder that significantly affects learning and behavior. Children with epilepsy are particularly vulnerable to educational problems and resultant academic underachievement. Co-morbidities like cognitive and behavioral problems contribute significantly for the problems at school. Both epilepsy and neuropsychological deficits may occur as different clinical manifestations of a common etiological process. Ongoing seizures themselves adversely affect the developing brain. Furthermore, psychosocial issues also contribute significantly to the problems at school. The effect of antiepileptic drugs is double edged in this setting. They may reduce the seizure burden and thus improve the cognitive function. However, these drugs also significantly affect the learning process. The treating pediatrician should be equipped to comprehensively address all these factors for an optimal outcome. Recent onset of educational problems in a child with epilepsy deserves immediate and aggressive evaluation and management.

Key words: *Antiepileptic drugs, Childhood epilepsy, Educational problems.*

From: Division of Child Neurology, Department of Neurology, Amrita Institute of Medical Sciences, Cochin, Kerala 682 026, India.

Correspondence to: Vinayan K.P. Fellow in Epileptology, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama 886, Aoi-ku, Shizuoka, 420-8688, Japan.
E-mail: vinayanputhenveettil@yahoo.co.in, vinayankp@aimshospital.org

Caring for a child with epilepsy involves facing multiple challenges simultaneously. Most of the time, it is much more than simply counting the number of seizures and adjusting the medications. A majority of these children will have associated learning and behavior disorders leading to significant difficulties at school(1). In this review, the relationship between epilepsy and educational problems in children is examined from multiple perspectives; including the epidemiological association, the effects on academic achievement, the importance of subclinical epileptiform discharges in learning and also the recent concept of state dependent learning disorders. Finally, the problems in the management of these children are discussed with special emphasis on the effects of antiepileptic drug (AED) administration.

Epidemiological Association

It is extremely difficult to estimate the exact burden of educational problems in childhood epilepsy for want of quality population data. Several terms such as learning disorders, learning disabilities, educational problems and scholastic problems have been used in different studies with overlapping meanings. The case definitions and inclusion criteria also differ across studies. Even though the majority of groups exclude children with mental retardation (MR) in defining learning disabilities, some authorities still prefer to consider them together(2). Most of the studies are hospital based with an inherent bias. So far, large-scale population studies on epilepsy have seldom classified subgroups with educational problems.

The rough prevalence of epilepsy and

educational problems in children is nearly similar (0.5%). Community studies in children with mental retardation have indicated prevalence rates of epilepsy ranging from 6% amongst children with mild MR (IQ, 50-70) to 50% in those with profound MR (IQ, <20)(2). In patients with MR and cerebral palsy, the cumulative risk for developing epilepsy has been estimated at 28, 31, and 38% at ages 5, 10, and 22 years(3).

Educational underachievement is considered to be the greatest academic complication in a child with epilepsy(4). Children with epilepsy experience educational problems more commonly when compared to the normal children of the same age(5, 6). In a well-conducted hospital based study from Delhi, 90 school-going children with epilepsy without previous history of neurodevelopmental problems were compared with 30 healthy controls. On detailed neuropsychological assessment, it was found that attention, concentration, immediate and remote memory were significantly impaired in school-going children with epilepsy when compared to normal children ($p<0.05$). Age of onset before 5 years and poor seizure control were significantly associated with neuropsychological impairment(7).

The risk for educational problems was found to be highest with symptomatic epilepsy associated with structural brain changes or genetic syndromes(8). Up to 90% of patients with Lennox-Gastaut syndrome or West syndrome have significant learning disorders(9). Even in children with idiopathic epilepsy and normal intelligence, the prevalence of educational problems was greater than expected, when compared to their sibling controls(6). In our own case series, 54% of children with benign epilepsy of childhood with centrotemporal spikes reported educational problems. Majority of these children had specific learning impairments on detailed neuropsychological evaluation(10). Even though, there are several studies showing deficits in learning process among children with epilepsy, no consistent pattern could be delineated. Problems have been found in a variety of areas including mathematics, spelling, reading, reading comprehension and general knowledge(11). These educational problems even tend to persist into adulthood(12).

The different factors, which can contribute to the educational problems in a child with epilepsy, are summarized in *Table I.*

Neuropsychological Deficits in Childhood Epilepsies

Many of the neuropsychological functions including cognition, attention and behavior can be affected in children with epilepsy for multiple reasons. These impairments can significantly affect the learning process. Several of these deficits may often co-exist in an individual patient.

Impairment in cognition

Cognition is a generic term embracing the mental activities associated with thinking, learning, and memory. It is the mental process of acquiring knowledge including aspects like

TABLE I– *Common Causes for Educational Problems in Children with Epilepsy*

1. Neuropsychological deficits
   - (*a*) Impairment in cognition
   - (*b*) Disorders of attention and behavior
   - (*c*) Specific learning disabilities - in reading, writing, spelling or mathematics
2. Psychosocial issues
   - (*a*) Reduced learning opportunities
   - (*b*) Poor self esteem
   - (*c*) Reduced expectations

awareness, perception, reasoning and judgment(13). Cognition is the single most important factor determining learning in children. Some studies have shown that the distribution of intelligence quotient scores of children with epilepsy as a whole is skewed towards lower levels(14,15). The prevalence of epilepsy is much higher in children with mental retardation as described above.

The commonest causes for cognitive deficits in children with epilepsy are given in *Table II*. Epilepsy and cognitive deficits may be the expression of a structural brain lesion, either congenital or acquired. Several genetic syndromes can have neurodevelopmental delay with significant mental retardation and refractory seizures. Tuberous sclerosis is a typical example. In such cases, the relationship between the ongoing epilepsy and the cognitive deficits becomes highly complex. However, it has been documented that ongoing seizure activity can further affect the developmental outcome in these situations (16).

Animal studies have shown that recurrent seizures result in long- term adverse effects in learning and memory. These behavioral changes are paralleled by changes in brain connectivity, dendritic morphology, excitatory and inhibitory receptor subunits, ion channels and neurogenesis. Surprisingly, these changes can occur even in the absence of overt cell loss(17). Recent studies have documented abnormalities even in intracellular functions of specific neurons after exposure to multiple seizures(18).

There is a growing emphasis on the cognitive abilities while classifying the epileptic syndromes of childhood. Broadly these are divided into benign syndromes and catastrophic syndromes (*Table III*). Benign epileptic syndromes are defined by the occurrence of infrequent or minor seizures and absence of cognitive deficits. On the other hand, the presence of resistant seizures, cognitive impairment or both is the rule in catastrophic syndromes. Perinatal adverse events and postnatal infections account for the majority of cases of catastrophic epileptic syndromes in India(19). This classification significantly helps the treating physician in prognostication, predicting future problems and developing a comprehensive management

TABLE II–*Causes for Cognitive Impairment in Children with Epilepsy*

A. Effect of Ongoing Seizures
Refractory epilepsies
Epileptic encephalopathies
Subclinical seizures
?Transitory cognitive impairment
B. Antiepileptic Drugs
C. Underlying Structural Brain Lesions

TABLE III–*Classification of Major Pediatric Epileptic Syndromes According to their Potential for Cognitive Impairment*

A. Benign Epileptic Syndromes
1. Benign neonatal familial convulsions
2. Childhood absence epilepsy
3. Benign epilepsy with occipital paroxysms
4. Benign epilepsy with centrotemporal spikes
5. Juvenile absence epilepsy
6. Juvenile myoclonic epilepsy
B. Catastrophic Epileptic Syndromes/ Epileptic Encephalopathies
1. Ohtahara syndrome
2. West syndrome
3. Dravet syndrome
4. Lennox Gastaut syndrome
5. Landau Kleffner syndrome
6. Continuous spike and waves in sleep (CSWS)

plan. However, it has been shown recently that minor neuropsychological impairment leading to educational problems may occur even in the so-called benign epileptic syndromes(10, 20).

Epileptic encephalopathies are a group of well-characterized catastrophic epileptic syndromes in which the ongoing deterioration of the cognitive functions of the child can be attributed to the persistent epileptic activity(21). West syndrome and Lennox Gastaut syndrome are typical examples. Clinical seizures are very few in number in Landau Kleffner syndrome and the syndrome of Continuous Spike and Waves in Slow wave sleep (CSWS). However, the neuro-developmental regression is associated with abundant subclinical epileptiform abnormalities in the EEG.

Subclinical epileptiform discharges and cognition

Epileptiform discharges during the performance of an EEG study, not accompanied by obvious clinical events are generally referred to as subclinical. However, it has been reported that sensitive methods of observation, notably continuous psychological testing, show brief periods of impaired cognitive function during such discharges. This phenomenon, called as transitory cognitive impairment (TCI), is seen in up to 50% of children who show discharges during a sophisticated computerized testing(22). Earlier reports suggested that such impairment occurs more in association with 3Hz spike and wave discharges. Irregular and focal spike and waves and slow wave bursts were found to have less effect(23). However, the effects of the focal EEG discharges were recently found to be site specific: lateralized discharges are associated with deficits of functions mediated by the hemisphere in which the discharges occur. Left sided discharges are known to produce performance errors in verbal tasks and right sided discharges, in nonverbal tasks (24).

TCI may contribute to the cognitive problems of some children with epilepsy leading to deficits that pass unrecognized. TCI is demonstrable in many cases of benign partial epilepsy of childhood, a disorder once thought to have no adverse neuropsychological effects(25). It can contribute to abnormalities of psychological test profiles and interferes with learning tasks, such as reading and mathematics. TCI may be associated with disorders affecting attention and behavior. Gonzalez-Garrido, *et al*., reported the occurrence of TCI in 36.2% of children with epilepsy during the execution of a go-no-go task. The epileptic group showed significantly higher numbers of behavioral errors and longer reaction times in relation to the control group(26).

An important issue for the practicing physician is whether TCI clinically impairs psychosocial function and academic achievement and, if so, whether drug treatment is desirable or effective. Several trials of antiepileptic treatment of TCI have demonstrated significant improvement in psychosocial function associated with suppression of discharges(25). Cognitive adverse effects of the antiepileptic drugs (AED) are a major concern. Over all, it can be said that the current clinical practice of "treating the patient and not the EEG" may need a modification at least in some selected situations. Further evidence is required for making firm conclusions and practice recommendations.

Disorders of Attention and Behavior

Epilepsy in children can be associated with multiple behavioral problems like mood fluctuations, hyperactivity, aggression,

irritability and reduced attention span(27). The presence of these problems will significantly affect the performance at school. Several studies have documented that children with epilepsy had significantly higher prevalence of behavioral problems compared to children with chronic illnesses not affecting the central nervous system(28,29). Follow-up studies of children with epilepsy have found a trend for the behavior to improve in those children with reduction in seizure frequency(30). Attention Deficit Hyperactivity Disorder (ADHD) is found to be strongly associated with epilepsy. McDermott, *et al.* reported hyperactivity in 28% of children with epilepsy when compared to 5% among controls(29).

Psychosocial Problems

One of the most common factors, usually overlooked, is the psychosocial environment of the child. In a recent study, Malhi and Singhi reported significant adjustment problems and compromised quality of life in children with epilepsy. The majority of parents in this study expressed major concerns regarding seizures, treatment by AED, future problems for the child and difficulties in parenting(31). Stigma resulting from the association of epilepsy and learning problems may lower the parental and teacher expectations(8). Decreased expectations can negatively affect the academic effort and consequently the performance. Seizures occurring in school can result in poor self-perception and reduced social interactions. It is better to have a proper neuropsychological assessment of the child to help the school personnel for planning the academic strategies.

State dependent Educational Problems

Aldenkamp, *et al.* prospectively studied a group of children with recent onset epilepsy and learning disorders with no pre-morbid history of mental retardation, dyslexia or ADHD. The crucial finding in this group was the relatively frequent demonstration of difficult-to-detect seizures, demonstrating that uncontrolled epilepsy can cause a decline in school performance even when the seizures are of short duration with only subtle symptoms. Multiple daytime absence seizures are a typical example. These problems are called 'state dependent' in view of their potential reversibility(32). Transitory cognitive impairment (TCI), described above may be another cause for state dependent learning problems. Psychosocial factors may also contribute to the development of this type of educational problems. Another potentiating factor may be the introduction of antiepileptic drugs with the resultant sedation, occasional visual blurring and cognitive effects. State dependent learning disorders become much more important in the benign epileptic syndromes where the basic intellectual functions are comparable to normal children. The identification of this condition is of added clinical significance in view of its potential reversibility. State dependent learning disorders, unless properly identified and managed in the earlier stages, can progress to permanent learning problems. Approach to a child with state dependent learning disability is outlined in *Table IV*(33).

Management Issues

Role of antiepileptic drugs (AED)

The effect of antiepileptic drugs on the learning process of a child with epilepsy is double-edged. On one hand, it can reduce the number of overt and subtle epileptic seizures leading to improvement in the cognitive functions and other learning processes. Reduction in the seizure count will in turn improve the psychosocial environment, providing additional benefit to the child.

TABLE IV–*Recommended Steps in Evaluation for Recent Onset Impairment in Scholastic Performance in a Child with Epilepsy* (33)

1. Detailed history from the parents and teachers to clearly identify the problem and the presence of probable undetected seizures
2. Neurological examination to find out AED adverse effects
3. Prolonged VEEG telemetry with awake and sleep recordings to identify subclinical seizures and CSWS
4. Monitoring of the antiepileptic drug levels in the serum
5. Detailed neuropsychological evaluation looking for the cognitive deficits and specific learning disabilities.
6. Psychosocial evaluation to identify problems at home and in school.

However, several case reports have shown time and again that learning processes are significantly affected by the intake of AEDs. It was difficult to demonstrate this effect through controlled studies due to various confounding variables(34). These effects are seen maximally at higher doses of AEDs or during polytherapy and prolonged intake. The problems can range from blurring of vision and diplopia due to minimal cerebellar dysfunction to excessive sedation and reduced psychomotor speed. Vigilance, memory and attention may also be affected leading to significant problems at school. The fact that these problems can sometimes arise even in the therapeutic ranges is all the more worrying(35). However, it is really difficult to assess whether the changes in behavior is related to the de novo effect of antiepileptic drugs or to the changes in seizure control. In the so called "release phenomenon", children with pre-existing mental retardation and behavior problems experience a rapid improvement in arousal and abilities when their seizures are controlled. This improvement initially occurs without the social skills and experience to use these new skills in a better way. As a result, these children suddenly appear hyperactive and uncontrollable(36). This situation can be mistaken for an adverse effect of the AED.

Studies on the individual drugs are difficult to evaluate because of the small patient numbers along with a wide variation in the dosage and duration of treatment and the treated epileptic syndromes(36). Generally, it can be said that all the AEDs have the potential for affecting the cognitive and behavioral domains. Of the classical drugs, phenobarbitone and benzodiazepines are the major ones reported to produce learning disorders. Phenytoin has also been found to cause impairment in memory and psychomotor speed. Cognitive and behavior problems on carbamazepine are relatively rare. However it can occasionally cause an increase in subtle seizures leading to learning problems(37). This is especially reported in benign epilepsies. Valproate can also produce learning problems in higher doses. The clinical experience of newer epileptic drugs in this group of children is very much limited and conflicting at present. So it is difficult to make firm conclusions and recommendations(38).

Use of stimulant drugs in ADHD and epilepsy

The use of stimulant drugs in the presence of epilepsy is considered to be potentially problematic in view of the propensity for reducing the seizure threshold. However, there is no definite clinical evidence to support this concern(36). On the contrary, available studies did not show any increase in seizure frequency during the administration of methylphenidate(39). So far atomoxetine is

Key Messages

- Epilepsy in children may be associated with significant problems in learning and behavior leading to academic underachievement.
- Multiple factors contribute to these educational problems, major ones being cerebral pathology, ongoing seizures, antiepileptic drugs and psychosocial issues.
- Judicious management of all these factors is essential for an optimal outcome.
- Recent onset educational problems in a child with epilepsy deserve immediate evaluation and management.

also found to be safe in this setting(36). However, controlled studies are lacking.

Role of epilepsy surgery

In view of the potential for the development of learning problems in children with recurrent seizures, epilepsy surgery in early childhood may be a feasible option in surgically remediable epileptic syndromes(33). The long-term adverse effects of antiepileptic drugs can also be avoided by an early surgical intervention.

Conclusion and Practice Recommendation

There is substantial evidence linking educational problems with childhood epilepsy. A child with history of seizures presenting with recent onset impairment in learning needs a very careful evaluation for state dependent learning disability. Children with associated specific learning disabilities and behavior problems need a detailed neuropsychological evaluation and appropriate remedial measures. Psychosocial issues if any should be thoroughly addressed. The optimal outcome depends on the coordinated multidisciplinary management strategies aiming 'far beyond mere seizure control'.

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