

Effect of antiepileptic drugs on behavioural and school underachievement in newly diagnosed idiopathic generalized childhood epilepsy

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ABSTRACT

Children with epilepsy are known to be prone to educational underachievement as a result of learning and behavioural problems. Identification of these comorbidities and their early intervention will go a long way in improving quality of life of children with epilepsy. The objective of this paper is to study the incidence of behavioural disorders (BD) and school underachievement (SU) in newly diagnosed generalized idiopathic epileptic children, and to determine association of behavioural disorders and school underachievement with different antiepileptic drugs. The design is prospective observational cohort study. Settings and duration is private multidisciplinary neuropaediatric clinics, from 1st September 2010 to 31st August 2013. 305 school going (7 to 16 years) children, 205 children with newly diagnosed idiopathic generalized epilepsy (study group) and 100 non-epileptic peers (50 siblings of epileptic children and 50 healthy children without family history of seizures or other chronic neurological illness (control group) were evaluated for BD and SU for over a period of four years. Chi Square Test was used for statistical analysis. The prevalence of BD and SU were present simultaneously in most of the patients. BD and SU were 11% in the study group, 10% in siblings of epileptic children, while in the control group without family history of epilepsy was 6% and this was statistically significant ($p < 0.05$). All epileptic children and their siblings have higher incidence of BD and SU as compared to their normal counterparts. These are associated with all currently used antiepileptic drugs (AEDs) in children. A holistic approach, comprising medical, educational and psychosocial counselling of families and placement of the child both in society and school should form integral part of management of idiopathic generalized childhood epilepsy (IGCE).

Keywords: Antiepileptic drugs, cognition, epilepsy, medication, neuropsychology, behavioural disorders, school underachievement.

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INTRODUCTION

The incidence of adverse effects is an important issue when prescribing AEDs, as some of the most effective medications for seizures are associated with a considerable degree of toxicity. Idiopathic generalized epilepsies (IGEs) are a relatively new category of disorders defined by strict clinical and electroencephalogram (EEG) features proposed by the International League against Epilepsy (ILAE) classification of epileptic syndromes (Anonymous, 1989). Approximately 70% of children with epilepsy will have

'idiopathic' epilepsy, where predisposing genetic factors have been identified, even whilst overt structural brain abnormalities are absent (Berg et al., 2008). This group of children generally display normal intelligence, participate in mainstream education and become seizure-free within a 2-year period (Aldenkamp et al., 2005). Epilepsy can impair an individual's functioning within work and educational domains (Bishop and Allen, 2003). It is now generally acknowledged that a subset of children with epilepsy will manifest some degree of cognitive

impairment. Cognitive impairments have been attributed to interactions among genetics, ongoing seizures, different epilepsy syndromes, subclinical epileptiform discharges, psychosocial issues, underlying causes of symptomatic epilepsy, and treatment with antiepileptic drugs (MacAllister and Schaffer, 2007; Bhise et al., 2010). Available antiepileptic drugs (AEDs) have the potential to exert detrimental effects on cognitive function and therefore compromise patient wellbeing (Chung et al., 2007; Bootsma et al., 2009). The effects of AEDs on learning and behaviour in children cannot be assessed unless these effects are analyzed within the context of all factors that can affect cognition and behaviour in children with epilepsy. Interactions among these factors could account for the wide interindividual variability in cognitive and behavioural effects of a particular antiepileptic. Therefore, it is essential that all contributory factors are considered and controlled for when studying the neuropsychological functioning of patients with epilepsy. Thus, studies of patients with idiopathic epilepsies may be useful in understanding whether cognitive impairment is related to the disease or it is due the side effect of medication (Hommet et al., 2001; You, 2012). Furthermore, only patients with intellectual abilities within the normal range, receiving monotherapy of AEDs that are not considered to cause significant adverse side effects on cognition, should be included. The paucity of studies investigating cognitive function in such well-defined homogeneous groups, using uniform neuropsychological tests, has led to the present study. Our main goal was, therefore, to evaluate systematically the BD and SU of children with newly onset idiopathic generalized epilepsy at presentation and after 2 years of treatment, when seizures were controlled (≤ 2 seizures over a year).

Theoretically, this information may contribute to the elucidation of the influence of the underlying 'seizure condition' on cognition. Clinically, it may contribute to the formation of intervention programmes that will improve the academic outcome of these children.

METHODOLOGY

Sample details

This was a prospective observational cohort study involving school going children with newly diagnosed idiopathic generalizes epilepsy, conducted over a period of four years at private multidisciplinary paediatric epilepsy clinics, the Brain Associates Institute Lahore. One hundred controls were selected, 50 from patients attending the outpatient clinics for minor ailments and 50 siblings of patients visiting for epileptic seizures. The 50 controls were healthy children without personal and family history of seizure and belonged to similar socioeconomic class as the epileptic subjects. The study subjects were 180 school going children with epilepsy selected randomly from those attending these neurology clinics for follow up and medication, who were fully investigated. All these patients were in remission (≤ 2 seizures over a year but no status epilepticus). Patients excluded from the study were: a) those with subnormal or mental retardation; b) patients with febrile seizures, syncope, hysterical seizures or pseudo seizures or seizures related to acute cerebral insult;

c) Patients with symptomatic and cryptogenic epilepsies; d) patients with psychopathologies at presentation; e) refractory to the monotherapy except 30 patients who were in remission on Valproate and Lamotrigine being used as a polytherapy. The age range studied here was broad (age: 7 to 16 years), and particular attention was paid to the use of tests that would allow administration of identical items across the entire age range as opposed to administering different tests of particular cognitive abilities to children in different age ranges.

Data collection

Detailed history of all children with special emphasis on schooling, academic performance, and peer and family relationship and behaviour problems was obtained and noted on a simple pre-structured proforma (Table 1), categorized as normal and inappropriate for age. Every normal component of the performa was scored as: normal = 0 and age inappropriate = 1. Patients were considered abnormal if they had ≥ 8 scores with at ≥ 2 scores from each category, with intra-ratter consensus. The questionnaire was pretested on 30 normal children for standardization and was fully explained and taught to parents. All children underwent a thorough clinical examination and a detailed neurological examination with special attention focused on their performance in school with regards to academics and behaviour at the start and 2 years after follow up. They were assessed by the same paediatric neurologist at the beginning and after 2 years of follow up.

Besides routine investigations, EEG, CT scan and MRI brain, serum antiepileptic drug levels were conducted wherever necessary. Twenty one channel EEG was done in every patient. EEG was reported by paediatric neurologist. The EEG findings were defined as, generalized epileptiform discharges, multifocal epileptiform discharges, focal epileptiform discharges, generalized slowing, and focal slowing and age appropriate normal EEG. Neuroimaging like CT scan / MRI, USG or X-ray skull were done in cases, where these were feasible and relevant to rule out symptomatic epilepsy. Any child with abnormal neuroimaging of brain was excluded from the study group. Appropriate antiepileptic drugs (according to the diagnosis) were given to all children with epilepsy under the supervision of paediatric neurologist. Conventional antiepileptic drugs (AED) were tried as the first and second AED later in cases of no response, newer AED were used in two groups. Valproic acid, Carbamazepine, Oxcarbamazepine, Lamotrigine and Levetiracetam were more commonly used drugs in this study.

Polytherapy (combination of AED) was given when monotherapy failed. Serum drug level was measured in some of the patients (due to financial constraints), when required. All relevant information from history, clinical examination, investigation, and follow-up visits were also collected from medical records in pre-designed sheets. Children with epilepsy in the study group were classified according to the seizure type by International League against Epilepsy (ILAE) classification- 1989, and only those who had primary generalized epilepsy were included in this study (Anonymous, 1989). Behaviour and school deterioration were assessed by detailed interview with parents and reviewing the school reports. Also, these children were observed and interviewed in detail and then decision about behaviour/school achievement was made in consensus with parents and school reports. Occasionally help was sought from educational psychologist for assessment of these children.

Statistical analysis

The results collected at the beginning and during the follow-up were processed using a Statistical Package for the Special Sciences (SPSS-V14). Statistical analysis was done using the repeated variance analysis for the changes of all data at 2 different time

Table 1. Assessment of behaviour and school achievement among children with epilepsy in association with different anti-epileptic drugs.

Behaviour	Before starting treatment		After 2 years of treatment	
	Age appropriate = 0	Age inappropriate = 1	Age appropriate = 0	Age inappropriate = 1
Behaviour at home				
With siblings				
With parents				
With guests				
Play				
Social maturation				
Behaviour at school				
Classmates				
Other students				
With teachers				
Play				
Social adoption acquisition				
School achievements				
Language				
Mathematics				
General knowledge				
Social maturation				
Extracurricular activities				

Abnormal Score = > 8 at least 2 components from each category.

Table 2. Distribution of psychopathologies among epileptic children at diagnosis and normal children of the same socioeconomic background.

No.	Category of children	Behavioral problems	School underachievement	Both behavioral problems + school underachievement
1	Epileptic children at diagnosis (205 = 100%)	25 (12%)	23 (11%)	23 (11%)
2	Normal children + family history of epilepsy in siblings (50 = 100%)	5 (10%)	5 (10%)	5 (10%)
3	Normal children with no family history of seizures (50 = 100%)	3 (6%)	3 (6%)	3 (6%)

intervals and $p < 0.05$ was accepted as significant (Table 2). Paired-t test was done for detection in which time interval the established significant value was present. The relationship between anti-epileptic drugs used, behavioural problems and school under achievement among the cohorts were statistically evaluated by using students' t' test and by using Pearson correlation analysis. A value of less than 0.05 was statistically significant.

RESULTS

The age of the epileptic children ranged from 7 to 16 years (mean 9.70 ± 1.42 years) and that of the controls from 6 to 16 years (mean 9.45 ± 1.60 years). Among the 50 healthy children with no family history of seizures, 3 (6%) had both behavioural problems and school underachievement,

whereas, behavioural problems were documented in 6 (12%) children and poor school performance in 5 (10%) children who were healthy but their siblings had epilepsy, 5 (10%) children had both behavioural and school problems. These psychopathologies were present among 25 (12%) among the epileptic children at presentation (Table 2). All epileptic children had normal behaviour and school performance at the beginning as 25 children with these disorders were excluded from the study group. The frequency distribution of the different syndromes were as: 1) Childhood absence epilepsies 10%; 2) Juvenile absence epilepsy 6%; 3) Juvenile myoclonic epilepsy 12%; 4) Grand mal epilepsy 30%; 5) Photosensitive epilepsy 4%; 6) Other idiopathic generalized epilepsies 38%. All these epileptic syndromes were associated with

Table 3. Distribution of psychopathologies among children with primary generalized epilepsies in association with different AEDs at 2 years of follow up (n = 180).

No.	Drug	No	Behavioral problems	School achievement problems	Behavioral and school achievement problems
1	Valproate	30	5 (16.6%)	5 (16.6%)	5 (16.6%)
2	Carbamazepine	30	5 (16.6%)	4 (13%)	4 (13%)
3	Oxcarbamazepine	30	4 (13%)	4 (10%)	3 (10%)
4	Levetiracetam	30	5 (16.6%)	4 (13%)	4 (13%)
5	Lamotrigine	30	3 (10%)	4 (10%)	3 (10%)
6	Valproate + Lamotrigine	30	7 (23%)	6 (20%)	6 (20%)
7	Total	180 (100%)	29 (16%)	27 (15%)	25 (14%)

childhood psychopathologies but without any specification.

One hundred and eighty children with epilepsy were studied and followed for 2 years, 110 were male and 70 were female with a male:female ratio of 1.57: 1. A similar trend was also noticed in the control group. Behavioural problems in the study group were commonest between 11 to 12 years (34%) followed by 15 to 16 years (32%), whereas in the control group there was a near equal distribution in all age groups. On the whole, 25 children had behavioural and school underachievement, comprising of 15 boys and 10 girls with male to female ratio of 1.5:1.

This cohort was consecutively selected from the large no of children with chronic epilepsy and comprised of 6 groups, each containing 30 patients being treated with Valproate, Carbamazepine, Oxcarbamazepine, Levetiracetam, Lamotrigine and poly therapy of Valproate and Lamotrigine. All these antiepileptic drugs (AEDs) caused significant psychopathologies among the IGEs without any specific association. These side effects were documented in highest percentage in patients treated with polytherapy (Valproate and Lamotrigine), followed by monotherapy comprising of Valproate, Levetiracetam and Carbamazepine. Minimal psychotherapies were seen in patients who were treated with Lamotrigine or Oxcarbamazepine, as monotherapies (Table 3). All these children were in remission at follow up of 2 years.

DISCUSSION

Cognitive and psychiatric difficulties exist before the first recognized seizure and are therefore independent of medications, seizures, and social reactions to seizures (Anonymous, 1989; Berg et al., 2008; Aldenkamp et al., 2005; Bishop and Allen, 2003). Several authors suggested that children with idiopathic generalized epilepsy may have behavioural and/or cognitive function impairment (MacAllister and Schaffer, 2007; Bhise et al., 2010). In agreement we found higher percentage of behavioural disorders (BD) and school underachievement assessed by a simple questionnaire (Table 1), not only children with

epilepsy but, also, this was found in their healthy siblings, indicating genetic proneness for poor school achievement among these children as compared with their counter parts with no family history of epileptic seizures (Table 2). All these indicate that neuropsychological impairment is an important comorbidity of chronic epilepsy, which is due to neurobiological factors that antedate the first seizure and influence cognition (Chung et al., 2007).

We observed a higher incidence of behaviour problems and school underachievement in relatively older children in our study cohort, as more than 60% of these were older than 11 years of age, with maximum frequency of these disorders in the age group of 11 to 12 years of age. In agreement, Chen et al. (2012) documented that older children were further behind in their achievement levels in word recognition, spelling, arithmetic, and reading comprehension than younger children (11). Bailet and Turk (Bailet and Turk, 2000), however, found no relationship between age at onset and neurocognitive scores. In a recent study of children with chronic epilepsy, Austin et al. (2001) also found that males were greater at risk for academic underachievement than females.

We documented that psychopathologies were almost equally prevalent among boys and girls. This is in contrast with others, as past studies suggest that gender and children's perceptions influence academic achievement in children with epilepsy. With regard to gender, a study of children with epilepsy found males to be more at risk for academic underachievement than females (Austin et al., 2002). In contrast, Howe et al. found male adolescents, including those with neurologic conditions, had higher achievement scores than did adolescent females (Howe et al., 1993).

The lack of consistency in this literature suggests a need for further evaluation of seizure variables in academic functioning, particularly as they might interact with other variables (that is, moderate other relations). All these controlled studies of children and adolescents with chronic epilepsy, but with substantially fewer years of recurrent seizures than the typical chronic adult population, have demonstrated that these patients may exhibit significant neuropsychological impairment, suggesting the influence of an early adverse neurodevelopmental impact on

cognition (Roeschl-Heils et al., 2002; Germano et al., 2005). A majority of these children will have associated learning and behavioural disorders leading to significant difficulties at school (Osborne and Dean, 2003). The exact cause of cognitive impairment in epilepsy has not been explored fully, but three factors clearly are involved: etiology, the seizures, and the “central” side effects of drug treatment (Aldenkamp, 2002). Available antiepileptic drugs (AEDs) have the potential to exert detrimental effects on cognitive function and therefore compromise patient wellbeing. We documented that a considerable percentage of children with epilepsy (CE) develop these disorders when followed for long time. However, the exact contribution by AEDs remains to be ascertained. The incidence of adverse effects is an important issue when prescribing antiepileptic drugs (AEDs), as some of the most effective medications for seizures are associated with a considerable degree of toxicity. Studies indicate that drug tolerability is a significant limiting factor in treatment maintenance, and drug retention rates are often determined by side-effect profiles (Aldenkamp, 2002; Chung et al., 2007). Cognitive impairment is a frequently occurring and may be an additional secondary consequence of treatment of epilepsy (Aldenkamp and Dodson, 1990; Dodson and Pellock, 1993). Presumably, we documented that all the AEDs used for 2 years caused these disorders in epileptic children. On the whole these disorders were documented as: behavioural disorders 15% (29/180, 15%), school underachievement 15% (27/180, 15%) and behaviour disorders and school underachievement 14% (25/180, 14%). On the whole or in association with the individual drug, these disorders were present simultaneously in most of the cases (Table 3). 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 (Schubert, 2005). Generally, it can be said that all the AEDs have the potential for affecting the cognitive and behavioural domains.

By selection of childhood primary generalized epilepsy, with normal cognition/behaviour at presentation, in remission after 2 years and treated with established monotherapy, we have concentrated on the unwanted effects of antiepileptic medication on cognitive function (school achievement) and/or behavioural functions. We documented higher percentage of such disorder among the children who were treated with Valproate and Lamotrigine as a polytherapy, followed by those who were treated with Valproate, Carbamazepine and Levetiracetam. They were observed in lesser percentage with Oxcarbamazepine and Lamotrigine (same percentage in both groups) (Table 3).

In a population-based cohort of adults with childhood-onset epilepsy, 76% had history of learning disability (Sillanpaa, 2004).

Some authors have noted negative influences on cognitive processes with the use of polytherapy leading to

high serum antiepileptic drug levels (Dodrill, 2004). In our study, there were a significantly greater (20%) number of patients using polytherapy group when compared to the medically controlled group on monotherapy (10 to 16%), but statistically this was not significant.

All established AEDs have “absolute” cognitive side effects (that is, all of the investigated drugs have cognitive effects when compared with patients requiring no treatment in the same group (Vermeulen and Aldenkamp, 1995), although minor changes have been reported in children (Schubert, 2005). These effects are generally considered to be safe for Valproate and Carbamazepine drugs, with a safe cognitive profile and mostly resulting in a mild, general psychomotor slowing (Aldenkamp et al., 1993; Henkin et al., 2005). In contrast to this, we found high percentage of psychopathologies among the patients being treated with Valproate and Carbamazepine. There are also studies which reported no negative effect of CBZ on cognitive functions in therapeutic ranges of serum levels (Trimble, 1987).

These results, like other studies, suggest a long-term risk of learning impairment for children with IGE, even if they have normal intelligence and their seizures are well controlled. Similar studies have been conducted for some of the newer AEDs (Gomer et al., 2007; Meador et al., 2007; Salinsky et al., 2004). Lamotrigine and Levetiracetam resulted in 48%, 42%, fewer cognitive side effects, respectively, compared with Carbamazepine. Their findings contrasted partially with findings of our study, which has shown that children with well controlled epilepsy (≤ 2 seizures per year) performed worse than healthy children in all cognitive domains, despite their normal cognition at presentation. However, Lamotrigine and Oxcarbamazepine were associated with lower percentage of such disorders among epileptic children treated for 2 years with these drugs. In agreement other studies have documented that Oxcarbamazepine may be the better option, as it has been associated with only minor cognitive impairments (Aikia et al., 1992). Similarly although some studies favour the use of Lamotrigine, they do not provide sufficient evidence to guide treatment (Pressler et al., 2006). In summary, the results of these studies indicate that OXC does not affect cognitive function in healthy volunteers and adult patients with newly diagnosed epilepsy. However, the effects of OXC on cognitive function have not been systematically studied in children and adolescents.

All these differences are partially due to the limitations in the designs of these studies; however, many of these studies report inconclusive findings. Although it will be necessary to overcome many programmatic and procedural hurdles, well-designed randomized prospective studies that are of adequate length to determine how AEDs ultimately relate to school performance and social adjustment are needed to firmly establish the cognitive and behavioural effects of AEDs in children (Loring and Meador, 2004). Because the cognitive

effects of AEDs can potentially be modified by discontinuing the drug, decreasing the dose, or switching to another medication, it is of critical importance to identify cognitive deficits that are potentiated by AED therapy. Because the control group (siblings and healthy children) was tested only once, longitudinal control data were not available for comparison after years of follow up of the same control. Finally, IQ is a well-established measure, it was neither done, nor cognitive and behavioural functions were done in all the patients by the neuropsychologist. Thus, despite the many strengths of this study (e.g., prospective enrolment and uniform psychometric assessment), its limitations do not allow any firm conclusion about AED effects on children's cognitive abilities to be made. Therefore, low achievement on a focused battery of academic measures can help identify children who are at risk and who need intervention. Proper and early identification is necessary to provide early developmental interventions, appropriate school programming, vocational counselling, supportive work settings, and a safe environment for promotion of independence across the life span.

CONCLUSION

Newly diagnosed untreated patients with epilepsy seem to be cognitively compromised before the start of antiepileptic drug medication. Cognitive impairment and mental disorders require further attention and essential therapy, which is important to the improvement of the quality of life in children with epilepsy. Hence, we recommend that CE should be closely monitored for development of behaviour problem and cognitive impairment. Newer antiepileptic drugs like Lamotrigine and Oxcarbamazepine, which have least affection on cognition and behavioural function, should be used. A holistic approach comprising medical therapy and psychosocial counselling of families and caretakers and placement of child both in the society and school are advocated as an integral part of management of epileptic children.

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