Factors associated with behavioural problems among children receiving anti-epileptic drugs

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Abstract

Children on anti-epileptic drug (AED) therapy have many health problems. Children with epilepsy are at a high risk for poor psychosocial outcomes, even without evident co-morbidities. Apart from the episodic seizures, multiple socio-cultural factors affect their behaviour and health. **Objective:** Objective of the present study is to find out factors associated with behavioural problems among children receiving anti-epileptic drugs. **Methodology:** A cross-sectional design was used in the present study. Data were collected from 275 children between 6 to 12 years, who were diagnosed with seizure disorder and on AED for a minimum of six months. Children along with their mothers were consecutively selected from paediatric neurology outpatient department of a tertiary care hospital. Personal interview was conducted with the mothers using Developmental Psychopathology Checklist (DPCL). Presence of specific psychopathology was identified based on the scores obtained for the sub domains of DPCL. Univariate analysis was done to findout cases and non-cases of each behavioural problem. Associated factors of behavioural problems were analyzed using bivariate logistic regression at 95% Confidence interval. **Results:** Age of onset of seizure disorder was a strong predictor variable of conduct disorders in children on AED therapy (*OR*: 4.059, 95% *CI*: 1.471-11.204, *p*=.007). Types of AED (*OR*: 1.860, 95% *CI*: 1.108 – 3.124, *p*= .019) had strong predictor association with learning problems among children. Good home care practice reduces learning problems in children receiving AED. (*OR*: 0.622, 95% *CI*: 1.471-11.204, *p*= .007). Similarly, duration of AED therapy (*OR*: 0.346, 95% *CI*: 0.127 -0.943, *p*: .038) has inverse effect on somatic complaints. No significant predictors were identified for ADHD or emotional problems. **Conclusion:** Behavioural problems among children receiving AED is associated with multiple factors. There is a complex interaction between all these factors. Identifying these pathologies and associated factors at the earliest along with effective treatment and control of seizures can significantly improve the quality of life of these children and their families.

Key words: Anti-epileptic drugs, behavioural problems, developmental psychopathology checklist, epilepsy, seizure disorder

Introduction

Epilepsy is one of the most prevalent neurological conditions in children. Population based studies conducted by Beilmann, Napa, Soot, Talvik, & Talvik, (1999) reported prevalence rates of 3.6 to 4.2 per 1000 for children in developed countries whereas Sridharan and Murthy (1999) found approximately double these rates in developing countries. The prevalence rates of epilepsy in India are similar to those of developed nations. According to Radhakrishnan et al. (2000), the prevalence rate of childhood epilepsy in Kerala is 4.9/1000. Attumalil, Anil, Vivek, Vijayakumar and Kunju, (2011) established that epilepsy is a common neurological disorder that affects nearly six lakh children under 14 years of age in the state of Kerala.

The goal of epilepsy treatment is to achieve a seizure-free state with minimal side effects from medication. Behavioural and psychological disorders in children with epilepsy have a multifactorial aetiology including biological and psychosocial factors. Anti-epileptic drugs remain one among many risk factors. Jim, Stancy, and Brooks, (2013) described two important mechanisms of

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drug induced behavioural changes, which were seizure control/forced normalization in psychosis and gamma-aminobutyric acid (GABA-ergic) effects in depression. Behavioural problems and affective disorders are the most commonly reported psychiatric adverse events of anti-epileptic drugs. According to Bettina (2003), psychosis is a relatively rare phenomenon, but severe psycho pathological complication is common in children undergoing anti-epileptic therapy.

Literature reveals a high frequency of behavioural problems in children with epilepsy. According to Berg, (2011), one third of children with epilepsy have a psychiatric diagnosis. This is supported by the findings of another study conducted in rural Kenya by Kariuki et al., (2012) to compare the prevalence of behavioural problems among children with epilepsy and healthy children (6.9 vs 4.9, $t = 4.7$, $p < .001$). Children with active epilepsy recorded more behavioural problems than those with inactive epilepsy (8.2 vs. 6.2, $t = -2.9$, $p = .005$). Although behavioural side effects are common with anti-epileptic drugs, its information in the nursing literature is sparse and these adverse effects are overlooked in the nursing care of children with epilepsy. Only a few studies related to psychosocial and behavioural problems of children receiving anti-epileptic drugs have been reported in Kerala. Since behavioural problems of children can result in a stressful family environment, knowledge of its associated factors can minimize its impact on family. This led to more rapid therapeutic adjustment and improvement in child and the caregivers' quality of life. **Objective:** The objective of the present study is to find out factors associated with behavioural problems among children receiving anti-epileptic drugs.

Materials and methods

The study used a quantitative research approach. Study was conducted in paediatric neurology department of Sree Avitam Thirunal (SAT) Hospital, Thiruvananthapuram. SAT Hospital being a tertiary care mother and child referral hospital, where children are referred from almost all southern districts of Kerala and nearby border districts of Tamil Nadu. Inclusion criteria for the study were children above six years diagnosed to have epilepsy as confirmed by a clinician and on anti-epileptic drugs for a minimum of six months. Children with significant co-morbid medical/neurological conditions and those with severe intellectual disability were excluded from the study.

Tool and technique

Study started after getting clearance certificate from institutional ethics committee. After obtaining an informed consent, personal interview was conducted with the mother to collect socio-personal data, clinical data, and their child's behavioural problems. Study used the following tools for collecting the data.

Tool 1 - Structured interview schedule to obtain socio personal and clinical data
Based on the findings from previous studies, baseline demographic information including age of child and mother, type of family, religion, domicile, education, occupational status of mother, and family income were included in the interview schedule.

Clinical data regarding type of seizure, seizure frequency and its severity were quantified using a semi-structured proforma. Frequencies of seizures during past one year were recorded. The seizure frequency of different types of seizures was dichotomized into low and high frequency. A low frequency seizure was labelled when the child had one to 20 episodes of simple partial seizures, one to four episodes of complex partial seizures, and one generalized tonic clonic seizure and one to 20 episodes of absence or myoclonic seizures during the last one year. More than the specified scores were labelled as high frequency seizures. This classification was done based on an internationally accepted guideline, which has been used in a previously published study conducted at Vellore by Datta, et al., (2005).

Seizure type was categorized into generalized and partial seizures. Type of AED (mono drug, poly drug), duration of AED (<1year, 1 to 3 years and >3 years), adherence to drug therapy (high, medium, low), and home care practice (good, average, poor) were categorized based on the scores obtained in the interview schedule.

Tool 2 - Developmental Psychopathology Checklist for Children
The Developmental Psychopathology Checklist (DPCL) is a standardized screening tool developed by Kapoor (2011) to assess psychopathology and behavioural problems in children. It is specifically simplified to suit the Indian Population. Permission was obtained from the author for using it for data collection. Interclass Correlation Coefficient (ICC) via analysis of variance was 0.96. It has 124 items under

seven subsections-hyperkinesis (Attention deficit hyperactive disorder), conduct disorders, learning problems, emotional disorders, obsessive-compulsive disorder (OCD), somatic symptoms, and psychoses. Among the sub domains, tool demands a need for reference and confirmation by a mental health expert for psychoses alone. The reliability co-efficient of Malayalam version of the tool was 0.80.

Bilingual experts did forward and backward translation and translated tools were finalized after pre-test. Test retest scoring of each tool was done. The reliability coefficient 'r' was calculated.

Statistical analysis

Presence of behavioural problems was based on the comparison of scores obtained in the sub domains of DPCL with the given standardized cut off scores. To differentiate cases and non-cases of each sub domains of psychopathology in DPCLunivariate χ^2 analysis was done. The variables that differed significantly at 0.1 level of significance in the univariate analysis were subjected to bivariate logistic regression. Odds ratio was calculated with 95% confidence interval. All the assumptions of bivariate logistic regression were found to be satisfied by the given set of data.

Results

Socio demographic characteristics

Among the children under study, 55.2% were above nine years of age. Average age of children under study was 9.2± 2.4. More than half of subjects (56.3%) were from urban domicile. Majority (78.2%) of subjects were from nuclear family. Socio-economic status of the family shows that 61.9% of subjects hold Above Poverty Line (APL) card issued by government whereas 38.1% have Below Poverty Line (BPL) card.

Table1:
Socio Personal Characteristics of Children Receiving Anti-Epileptic Drugs

N= 270

Socio personal characteristics of children		Frequency	Percentage
Age in years	6 - 9	121	44.8
	>9	149	55.2
	Median ± SD	9.2± 2.4	
Domicile	Urban	152	56.3
	Rural	118	43.7

Socio personal characteristics of children		Frequency	Percentage
Type of family	Nuclear	213	78.4
	Joint	7	2.6
	Extended	50	18.5
Family income	BPL	103	38.1
	APL	167	61.9

Clinical characteristics of children with epilepsy

Mothers of 17.4% children on anti-epileptic drugs had a history of antenatal problems. Average age at onset of seizure disorder was five years. Majority of children (69.3%) was diagnosed with subtypes of partial seizures. Among the children under study, 26.3% had reported severe seizure frequency, 43% were on anti-epileptic drugs for more than three years. For the type of AED, 47.8% of children were on mono drug therapy and 52.2% were on poly drug therapy.

Majority of subjects (42.6%) had a high adherence to anti-epileptic drug therapy whereas 27.8% of subjects scored medium adherence and 15.6% reported low adherence to anti-epileptic drugs. More than half of subjects (53.3%) reported good home care practice whereas 14.1% were poor in their home care practice. Among children receiving AED from six years to 15 years, 54.8% had learning disability and 44.4% children had emotional problems, 21.5% had ADHD. Conduct disorders were found among 9.3% of children and somatic disorders were seen among 4.2% of children.

Table 2:
Factors Associated with Behavioral Problems: Univariate Analysis

N=270

Variable		Case		Non-Case		χ^2	p value
		n =61	%	n =209	%		
Antenatal health problems	Present	15	31.9	32	68.1	2.828	.071
	Absent	46	20.6	177	79.4		
Adherence to drug therapy	High	21	16	110	84	13.088	.001*
	Medium	22	22.7	75	77.3		
	Low	18	42.9	24	57.1		
Home care practice	Good	30	20.5	116	79.5	6.655	.036*
	Average	16	18.8	69	81.2		
	Poor	15	38.5	24	61.5		
Conduct disorder							
		(n =25)		(n =245)			
Duration of AED	≤1 year.	4	5.4	70	94.6	5.008	.082
	1 – 3 years.	5	6.2	75	93.8		
	> 3 years.	16	13.8	100	86.2		

Variable		Case		Non-Case		χ^2	p
		n =61	%	n =209	%		value
Age of onset of seizure	<5 years.	20	14.3	120	85.7	8.744	.002*
	>5 years.	5	3.8	125	96.2		
Adherence	High	10	7.6	121	92.4	5.683	.05*
	Medium	7	7.2	90	92.8		
	Low	8	19	34	81		
Learning disability							
		(n = 148)		(n = 122)			
Age of onset of seizure	<5 years.	84	60	56	40	3.156	.049*
	>5 years.	64	49.2	66	50.8		
Seizure frequency	Lesser	98	49.2	101	50.8	9.474	.001*
	Severe	50	70.4	21	29.6		
Type of AED	Mono drug	77	59.7	52	40.3	2.370	.078
	Poly drug	71	50.4	70	49.6		
Home care practice	Good	70	47.9	76	52.1	7.873	.020*
	Medium	50	58.8	35	41.2		
	Poor	28	71.8	11	28.2		
Family income	Lesser	65	63.1	38	36.9	5.650	.05
	Severe	83	49.4	84	50.6		
Emotional problems							
		(n = 120)		(n = 150)			
Age of the mother	≤35 years.	79	48.2	84	51.8	2.349	.079
	>35 years.	41	38.7	65	61.3		
Gender	Boy	74	78	78	51.3	2.532	.071
	Girl	46	39	72	61.0		
Type of seizure disorder	Generalized	30	36.1	53	63.9	3.343	.044*
	Partial	90	48.1	97	51.9		
Seizure frequency	Lesser	83	41.7	116	58.3	2.294	.085
	Severe	37	52.1	34	47.9		
Somatic complaints							
		(n = 12)		(n = 258)			
Duration of AED	≤1 year.	2	2.7	72	97.3	9.013	.011*
	1 – 3 years.	0	0	80	100		
	> 3 years.	10	8.6	106	91.4		
Home care practice	Good	6	4.1	140	95.9	8.619	.013*
	Medium	1	1.2	84	98.8		
	Poor	5	12.8	34	87.2		
Type of seizure disorder	Generalized	7	8.4	76	91.6	4.491	.04*
	Partial	5	2.8	182	97.3		

Univariate analysis was done to compare children on AED with behavioural problems and without behavioural problems. Adherence to drug therapy (χ^2= 13.088, p= .001) and homecare practice (χ^2= 6.655, p= .036) were found to have significant difference among cases and non-cases of ADHD among children receiving AED at .05 level of significance. Age of onset of seizure disorder (χ^2= 8.744, p= .002) and adherence to drug therapy (χ^2= 5.683, p= .058) were found to have significant association with conduct disorders among children receiving AED. Among children with learning

disability, significant difference in cases and non-cases were found with age of onset of seizure disorder (χ^2= 3.156, p= .049), seizure frequency (χ^2= 9.474, p= .001) and home care practice (χ^2= 7.873, p= .020). Emotional problems in children on AED had significant association with their mother's age (χ^2= 11.573, p= .000), and type of seizure disorder (χ^2= 3.343, p= .044). For children with somatic complaints significant difference was found with treatment duration (χ^2=9.013, p= .011), home care practice (χ^2=8.619, p= .013) and type of seizure disorder (χ^2=4.491, p= .04).

Table 3:

Factors Associated with Behavioural Problems: Bivariate Analysis

Variable	B*	S.E*	Significance	OR	Confidence Interval	
					Lower	Upper
Conduct disorders						
Age of onset of seizure	1.401	0.518	.007**	4.059	1.471	11.204
Learning Problems						
Type of AED	0.621	0.264	.019*	1.860	1.108	3.124
Home care practice	-0.475	0.187	.011*	0.622	0.431	0.898
Somatic complaints						
Duration of AED therapy	-1.060	0.511	.038*	0.346	0.127	0.943

*B- Intercept (co-efficient for the constant), S.E-Standard Error around the co-efficient for the constant

On bivariate analysis, age of onset of seizure disorder was a strong predictor variable of conduct disorders in children on anti-epileptic drug therapy (*OR*: 4.059, 95% *CI:* 1.471-11.204, p= .007). Type of AED (*OR*: 1.860, 95% *CI:* 1.108 – 3.124, p= .019) had strong predictor association with learning problems among children. Home care practice was found to have a protector effect on learning problems (*OR*: 0.622, 95% *CI*: 1.471-11.204, p= .007). Good home care practice reduces learning problems in children receiving AED. Similarly, duration of AED therapy (*OR*: 0.346, 95% *CI*: 0.127 -0.943, p: .038) has inverse effect on somatic complaints. There were no significant predictors for ADHD or emotional problems.

Discussion

Present study focused to find out the associated factors of behavioural problems among children receiving anti-epileptic drugs. In a hospital based prospective, study of children admitted with acute episode of seizure in

a tertiary care centre in South India, Datta S S et al., found almost a similar socio personal pattern among children. Another important finding was majority (42.6%) of participants had a high adherence to anti-epileptic drug therapy. Among the study participants, 22.7% of subjects scored medium adherence and 5.8% reported low adherence to anti-epileptic drugs. SAT hospital being a referral and service centre, more children from the middle socio-economic group with good awareness regarding importance of childhood seizures came for consultation.

Seizure disorder and AED in children is associated with considerable psychopathology. Present study recognized ADHD (21.5%), conduct disorders (9.3%), learning disability (54.8%), emotional problems (44.4%) and somatic disorders (4.2%) as important behavioural problems among children. In a south Indian study conducted at Vellore by Datta, et al., (2005) the prevalence of psychopathology scores as assessed by the Childhood Behaviour Checklist among children with seizure disorder was 53.8%. In another hospital-based study conducted at Karnataka by Philip, Patil, and Kamate, (2016), 23.4% of children with epilepsy were found to have ADHD compared to 3 – 5 % in general population which supports the findings of the present study. In a study conducted by Fastenau, Dunn, and Austin (2009) to identify the rates of learning disability (LD) among children with seizure disorder, 41% to 62% exceeded cut-offs in at least one academic area that supports the present finding of 54.8%. In the present study, learning disability has significant association with type of anti-epileptic drugs whereas somatic disorders were significantly associated with duration of illness. A similar association was found in Vellore study (Datta, 2005). In a review article published by Wei and Lee (2015), young age at onset, symptomatic cause and continued treatment of AEDs were reported to be independently associated with cognitive outcome. Similarly, Malhotra, Singh, & Mohan, (2005) reported that age at onset of disorder and intelligence were significantly higher among children with somatic disorders. Psychopathology in children with seizure disorder is due to the interaction of multiple factors including physical health problems, developmental problems, socio-demographic factors and treatment itself. Children develop psychopathologies, as the exposure to the risk factors during their developmental

stages is more. Many previous studies have proved that anti-epileptic drugs also have additive effects, even at therapeutic concentrations, causing behavioural problems.

Limitations
Present study is a tertiary care hospital based study that used a cross sectional design. Among the clusters of Developmental Psychopathology Checklist, researcher could not confirm autism and psychosis as the tool itself limits its usage in confirmation of these psychopathologies. Data was ascertained only through parent reports.

Conclusion
Behavioural problems among children receiving AED is associated with multiple factors. There is a complex interaction between all these factors. Identifying these pathologies at the earliest along with effective treatment and control of seizures can significantly improve the quality of life of these children and their families. It is important to address behavioural problems and its impact on caregivers among children receiving AED along with their seizure disorder. Health care providers must focus on a holistic approach while treating children with seizure disorder.

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