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Original Article

Risk of Seizures Associasted with Non-Adherence to Antiepileptic Drugs

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ABSTRACT

Introduction: *Epilepsy is one of the most common neurological diseases worldwide. In Bangladesh, the prevalence of epilepsy in children was 8.2/1000 population. Among many factors, non-adherence to AEDs is an important modifiable factor for seizure control. This study aimed to assess the risk of seizures associated with non-adherence to antiepileptic drugs.* ***Methods & Materials:*** *This cross-sectional study was conducted at the Department of Pediatric Neurology and Development; National Institute of Neurosciences and Hospital (NINS&H), Dhaka, from January 2022 to December 2022. A total of 250 children were selected as study subjects by systematic random sampling without a sampling frame technique. After assessment by MMAS-8, children with epilepsy were categorized into two groups, AEDs adherent (n_1) and non-adherent group (n_2). Statistical significance and confidence interval were set at p<0.05 and 95% level respectively.* ***Result:*** *In this study among 250 children with epilepsy, 56.8% (n=142) children were found non-adherent to AEDs. There was a significant (p<0.05) association between drug non-adherence and higher maternal education as well as poor seizure control. Forgetfulness (p=0.00, OR=5.00), child's refusal to take AEDs (p=0.00, OR=5.29), and long duration of treatment (p=0.017, OR=2.33) were found to increase the risk of non-adherence.* ***Conclusion:*** *Non-adherence to antiepileptic drugs (AEDs) significantly increases the risk of uncontrolled seizures, with key contributing factors including forgetfulness, child refusal to take medication, and long treatment duration. Higher maternal education and lower family income were also associated with higher non-adherence rates. Logistic regression analysis confirmed that forgetfulness and child refusal to take AEDs were the strongest independent predictors of non-adherence.*

Keywords: *Seizure, Risk factor, Non-adherence, Antiepileptic Drugs*

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INTRODUCTION

Epilepsy is a brain disease characterized by abnormal brain activity causing seizures or unusual behavior, sensations, and sometimes loss of awareness. It carries neurological, cognitive, psychological, and social consequences and accounts for a significant proportion of the world's burden of disease [1]. In 2014, the International League Against Epilepsy (ILAE) revised the definition of epilepsy 'as a disease of the brain defined by any of the following conditions: i) At least two unprovoked (or reflex) seizures occurring > 24 h apart. ii) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (At least 60%) after two unprovoked seizures, occurring over the next 10 years iii) Diagnosis of an epilepsy syndrome [2]. In Bangladesh, a nationwide survey showed the prevalence of epilepsy per 1000 is 8.4 and the prevalence in children aged <18 years was similar to adults which is 8.2/1000 [3]. The principle of management should be individualized and the selection of treatments should aim to control symptoms as well as to prevent other complications [4]. The aim of antiepileptic drug (AED) therapy is to achieve freedom from seizures. Patients fail to achieve their goals and outcomes when they fail to adhere to the drug regimen or when a less-than-adequate drug regimen is prescribed. Most of the treatment of epilepsy is aimed at creating a balance between the prevention of seizures and the minimization of side effects to a level that the patient can tolerate [5]. There are many factors behind poor control or uncontrolled seizures like lack of motivation about the disease, unavailability of drugs, irregular intake of anti-epileptic drugs, stopping AEDs willingly after transient control of seizures, lack of knowledge about the disease, unemployment, lower educational status, residence in rural area, earlier age of onset of seizure, higher initial seizure frequency etc. [6]. Poor adherence to prescribed

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medication is the primary reason for unsuccessful epilepsy treatment [7]. In children with epilepsy, non-adherence remains a significant challenge in achieving the crucial therapeutic goal of complete seizure control [8]. Non-adherent patients experience an increase in the number and severity of seizures, which leads to a higher incidence of emergency room visits, hospital admissions, more tendency to injuries and fractures, as well as higher inpatient, outpatient, and total health care costs [9]. Non-adherence is defined as, 'the inclination to forget, avoid, or discontinue medicine or to alter the dose from that prescribed by the healthcare provider' [10]. Non-adherence can range from occasionally missing a dose to consistently failing to follow medication regimens. Among chronically ill children, its negative effects include increased morbidity and mortality, reduced cost-effectiveness due to wasted medications, higher frequency of clinic visits, emergency room admissions, and hospitalizations, as well as potential bias in clinical trials evaluating new therapies [11, 12]. Non-adherence to medication is common among children with epilepsy and it hampers the key therapeutic goal of seizure control. Factors associated with non-adherence may include low socioeconomic status/ financial constraint, forgetfulness, multiple drug therapy and long duration of treatment, lack of improvement, medication side effects, inadequate counselling to patient or parents during initiation of treatment and sometimes decisions based on personal judgments about the effectiveness of the proposed treatment [13, 14]. AED medication adherence can be measured by different methods like, measuring drug level, pill count, pharmacy refills, patient's self-report etc. Each method has its own advantages and limitations [15]. In this study, Morisky medication adherence scale eight items (MMAS-8), a self-report measure of medication taking behavior designed by Morisky et al is used [16]. MMAS-8 is widely used because some studies have provided evidence of good psychometric properties of the scale, high sensitivity (74.1%) and specificity (38.3%) [17, 18]. Adherence to antiepileptic medication remains a significant challenge in developing countries like Bangladesh, where various socioeconomic and healthcare-related factors contribute to poor compliance. This study aimed to assess the risk of seizures associated with non-adherence to antiepileptic drugs.

METHODS & MATERIALS

This cross-sectional study was conducted at the Department of Pediatric Neurology and Development; National Institute of Neurosciences and Hospital (NINS&H), Dhaka, from January 2022 to December 2022. Diagnosed cases of Epilepsy (based on ILAE) who visited OPD or were admitted to the inpatient department of Paediatric Neurology, National Institute of Neurosciences and Hospital, Sher -E- Bangla Nagar were considered as the study population. A total of 250 children were selected study subjects by systematic random sampling without a sampling frame technique. Screening was done by thorough history and clinical assessment. Data was collected by face-to-face interview through a preformed semi-structured questionnaire containing information about the age of onset & type of epilepsy, clinical diagnosis, name & dosage of AEDs & status of seizure. Medication non-adherence was assessed by the Morisky Medication Adherence Scale with eight items (MMAS-8) based on self/caregiver reports. After assessment by MMAS-8, children with epilepsy were categorized into two groups, AEDs adherent (n_1) and non-adherent group (n_2). Data analysis was carried out using Statistical Package for Social Sciences (SPSS- 23). Continuous variables were expressed as the means ± SD, and categorical variables were expressed as percentages, frequencies, and proportions. Means were compared using Student's t-test for two groups. Proportions were compared using the chi-square test. Then Logistic regression analysis was performed to determine the factors influencing the risk of seizures. Statistical significance and confidence interval were set at $p<0.05$ and 95% level respectively. Written approval was taken from the concerned authority (ethical committee of NINS&H and BCPS) and the department with due procedure. Informed written consent was taken from the parents or legal guardians.

Inclusion criteria:

- Children with epilepsy and
- Who had been on at least one antiepileptic drug for 1 year or more before the study and
- Aged >1 year to under 18 years.

Exclusion criteria:

- Patients with comorbid chronic illnesses requiring daily medication (eg, asthma, kidney diseases, chronic liver disease, etc).

RESULTS

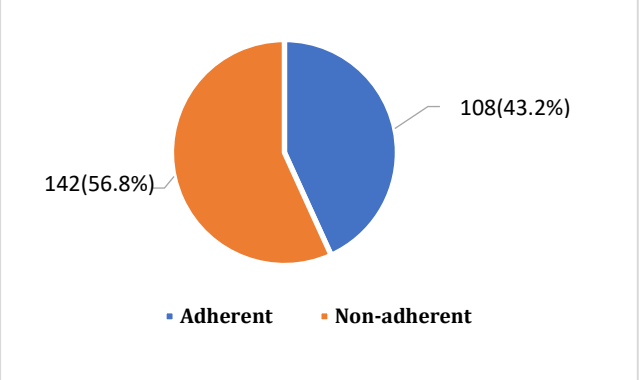

Figure – 1: Distribution of children according to AEDs non-adherence

Figure 1 shows, that out of 250 participants, 142 (56.8%) had non-adherence, while 108 (43.2%) patients/ respondents had adherence to AEDs.

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Table – I: Comparison of sociodemographic characteristics between the studied groups (*n*=250)

Variables	Adherent Group n_1=108(43.2%)	Non-adherent Group n_2=142(56.8%)	p-value
Age group (years)			
1-5	46(42.6%)	61(43.0%)	-
>5-10	40(37.0%)	52(36.6%)	
>10-15	22(20.4%)	29(20.4%)	
Total	108(100.0%)	142(100.0%)	
Mean±SD	6.65±3.84	6.67±3.74	0.922
Gender			
Male	70(64.8%)	97(68.3%)	-
Female	38(35.2%)	45(31.7%)	
Male: female ratio	1.8:1	2.2:1	0.561
Residence			
Urban	70(64.8%)	89(62.7%)	0.728
Rural	38(35.2%)	53(37.3%)	
Maternal/caregiver education			
No formal education	13(12.0%)	12(8.5%)	0.012*
Primary	65(60.2%)	62(43.7%)	
Secondary/SSC	21(19.4%)	42(29.6%)	
Above secondary	9(8.3%)	26(18.3%)	
Father's occupation			
Service	41(38.0%)	32(22.5%)	0.176
Business	63(50.4%)	84(59.2%)	
Others (farmers, shopkeepers)	24(19.2%)	26(18.3%)	
Monthly family income (Tk.)			
<10000 Tk.	34(31.4%)	68(47.9%)	0.026*
10000 – 30000 Tk.	52(47.9%)	48(33.8%)	
>30000 Tk.	22(20.4%)	26(18.3%)	

*= significant

Table I shows the majority of children were between 1- 5 years, that is 42.6% in the adherent group and 43.0% in the non-adherent group. Comparing between mean ages of the two groups showed no statistical significance. In both adherent and non-adherent groups majority of children were male, 64.8% and 68.3% respectively, but that difference was not statistically significant. Comparing the distribution of study subjects by residence no statistical difference was observed between the two groups. The highest percentage of respondents belonged to urban areas in both groups. 72.2% of mothers in the adherent group had primary-level education or had no formal education. Whereas, in the non-adherent group, primary level education or no formal education was found in 52.2% of mothers. This difference was statistically significant. Majority of the fathers' profession was business in both groups (50.4% in the adherent group and 59.2% in the non-adherent group) and the difference between the groups was not statistically significant. Regarding family income, statistically significant differences were present between the two groups. The adherent group had higher monthly family income (47.9% had 10,000-30,000 tk and 20.4% had >30,000 tk) than the non-adherent group (<10000 tk. in 47.9% and 10,000-30,000 tk in 33.8% cases).

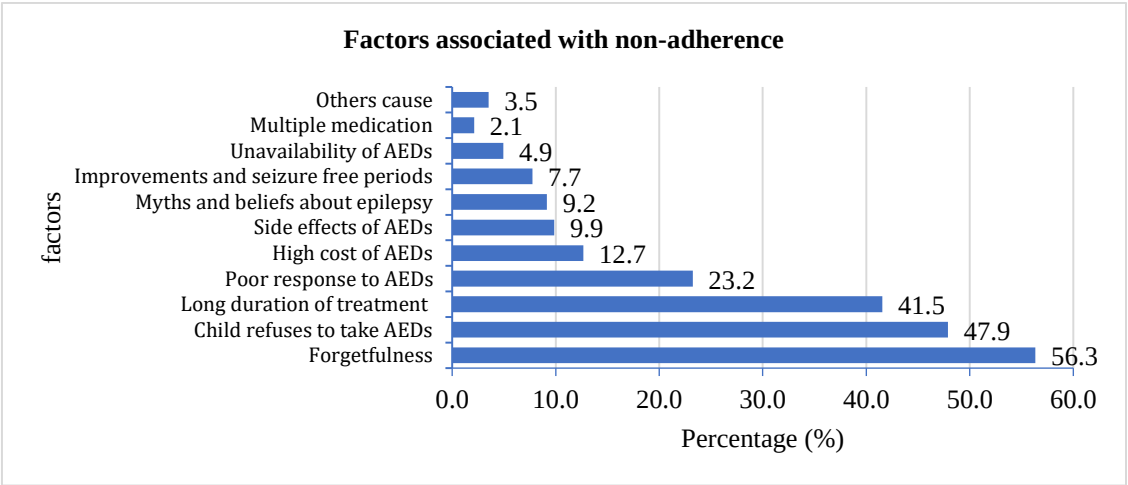

Figure – 2: Bar diagram showing the factors associated with non-adherence

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Figure II shows the factors associated with non-adherence to AED. Forgetfulness was the most common factor for non-adherence (56.3%), followed by child's refusal to take AEDs (47.9%), long duration of treatment (41.5%), poor response to AEDs (23.2%), high cost of drugs (12.7%), side effects of drugs (9.9%), myths and beliefs about epilepsy (9.2%), improvements & seizure-free periods (7.7%).

Table – II: Association between drug non-adherence and seizure control (*n*=250)

Seizure status	Adherent Group n_1=108(43.2%)	Non-adherent Group n_2=142(56.8%)	p-value
Controlled	91(84.3%)	10(7.0%)	<0.001*
Not Controlled/ uncontrolled	17(15.7%)	132(93.0%)	
Total	108(100.0%)	142(100.0%)	-

p-value obtained by Chi-square test, *= significant

Table II shows that in the adherent group, the seizure was controlled in 84.3% of participants and in the non-adherent group it was 7%. The Seizure control was significantly higher in the adherent group than in the non-adherent group.

Table – III: Analysis of risk factors associated with non-adherence to AEDs

Risk factors	B	S.E.	p-value	OR	95% C.I	
					Lower	Upper
Maternal education (secondary & above)	-2.156	.508	.000*	.116	.043	.313
Income (<30,000 Tk.)	.086	.471	.856	1.089	.432	2.744
Duration of seizure (> 1 minute)	.832	.635	.190	2.299	.662	7.986
Seizure status (uncontrolled)	-3.961	.467	.000*	.019	.008	.048

*= significant, bivariate logistic regression was done

Table III shows, the binary logistic regression analysis of the previously statistically significant variables, where higher maternal education (secondary & above) and uncontrolled seizures were associated with non-adherence to AEDs.

Table – IV: Analysis of risk of seizures concerning non-adherence to AEDs

Factors	B	S.E.	p-value	OR	95% C.I	
					Lower	Upper
Forgetfulness	1.611	.324	.000*	5.009	2.656	9.445
Child refusal to take AEDs	1.666	.359	.000*	5.290	2.617	10.69
Long duration of treatment	.847	.354	.017*	2.333	1.166	4.667
Poor response to treatment	-.747	.388	.055	.474	.221	1.015

*=significant, bivariate logistic regression was done

Table IV shows, the binary logistic regression analysis of the factors associated with non-adherence. Here, forgetfulness (p=0.00), child refusal to take medication (p=0.00), and long duration of treatment (p=0.017) were independently associated with non-adherence. Forgetfulness (OR=5.009), child's refusal to take medicine (OR=5.290), and long duration of treatment (OR=2.333) increase the risk of seizures concerning non-adherence.

DISCUSSION

In this study, 56.8% of children with epilepsy (CWE) showed non-adherence to AEDs. This finding is similar to the 61.3% found in another study on adults from Bangladesh by Chowdhury et al in 2020 and 44.8% in Nigeria [6, 13]. A higher level of low adherence (72.5%) to AEDs was found by Mohammad et al in 2020 in a national household survey done on both children and adults in Bangladesh [3]. But studies are showing lower rates of non-adherence to AEDs, 27.7% in Iran and 20.5% in Jordan [14, 15]. The present study showed that the maximum children's age was between 1-5 years in both groups, 42.6% in the adherent group and 43.0% in the non-adherent group. The mean age in the two groups was almost similar (6.65±3.84 and 6.67±3.74 respectively) without any statistical significance. Similar results were found in different studies done in Iran and Jordan where the mean age of the participants was 7±4.6 years and 7.3±4.0 years respectively [15, 19]. A bit higher age group was found in another study done in Nigeria, which showed maximum (47.9%) of children were in the 6-10 years age group [13]. In both adherent and non-adherent groups, the majority of children were male, 64.8% and 68.3% respectively. Similar findings were found in a study done in Nigeria (male 52.1%, female 47.9%) and in an Iranian study without statistical significance (male:female=1.29) [13, 14]. Equal gender distribution was present in another two studies in Bangladesh[3,4] and one study in Jordan [19]. This study showed, in both adherent and non-adherent groups that maximum (64.8% and 62.7% respectively) CWE came from urban areas which was not statistically significant. In a

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national household survey done in Bangladesh stated almost similar findings [3]. However, another study done in our country showed, that the majority of patients were from rural areas (62.3%) which was not found to be significantly associated with adherence [4]. So, it may be understood that epilepsy is prevalent in both urban and rural areas. In this study, a significantly higher number of mothers had a primary level of education in the adherent (60.2%) group than that of the non-adherent (43.7%) group. Mothers having an educational level of and above secondary were more in the non-adherent group (47.9% versus 27.7%). These findings are similar to another study done by Chowdhury et al in 2020 [4]. Another study in Nigeria revealed that most of the caregiver of CWE had secondary level education without any significant difference between adherent and non-adherent group [13]. These results show that, education may have a role in AEDs adherence but higher education does not help with drug adherence. Most of the fathers' profession were business (50.4% in adherent group and 59.2% in non-adherent group). Others were service holder, farmers or shopkeepers. Another study done by Dima SA and Shibeshi MS found that, majority of parents were employee/ service holder, followed by merchants and farmers [20]. Another study done in Uganda revealed, caregiver (mother/other) having an occupation had increased likelihood of non-adherence to AEDs [21]. Father's occupation did not affect child's AEDs adherence directly. Family income of participants was less than 10000 tk. in 47.88% cases and 10,000-30,000 tk in 33.8% cases in the non-adherent group. In adherent group, monthly family income was significantly higher than the non-adherent group, that is, 47.9% had 10000-30000 tk/month and 20.4% had higher income. These observations were similar to the previous studies, that is, higher family income helped better AEDs adherence among children [13, 20, 22]. But another study done in Nigeria showed different findings, where all the patients in high adherence were belonged to relatively low income group [23]. In the present study, among the factors associated with non-adherence to AEDs, forgetfulness was the most common factor (56.3%), followed by child's refusal to take AEDs (47.9%), long duration of treatment (41.5%), poor response to AEDs (23.2%), high cost of drugs (12.7%), side effects of drugs (9.9%), myths and beliefs about epilepsy (9.2%), improvements & seizure free periods (7.7%). After logistic regression, forgetfulness, child refusal to take medication and long duration of treatment were found to increase the risk of seizures in relation to non-adherence. Another Bangladeshi study found forgetfulness (35%), lack of counseling (27.67%), cost of drug (24.5%), false belief (23%), drug unavailability (10.2%), lack of benefit (8.3%) and fear of side effects (7.9%) were the factors associated with non-adherence [4]. In a Nigerian study, they found low socioeconomic status (49.4%), forgot to take drugs 936.8), lack of improvement (17.2%), multiple drug intake and long duration of therapy to be the causes of non-adherence [13].

Limitation of the study

Being a single-center study, the findings may not be generalizable to the entire population. Additionally, recall bias from respondents could have influenced the accuracy of the reported adherence patterns. There are numerous other factors contributing to non-adherence that were not addressed in this study, which may limit the comprehensiveness of the analysis. Furthermore, the cross-sectional design restricts the ability to establish a direct cause-and-effect relationship between non-adherence and seizure risk.

CONCLUSION

Non-adherence to antiepileptic drugs (AEDs) significantly increases the risk of uncontrolled seizures, with key contributing factors including forgetfulness, child refusal to take medication, and long treatment duration. Higher maternal education and lower family income were also associated with higher non-adherence rates. Logistic regression analysis confirmed that forgetfulness and child refusal to take AEDs were the strongest independent predictors of non-adherence.

RECOMMENDATION

To improve adherence to antiepileptic drugs (AEDs) and reduce seizure risk, targeted interventions should focus on caregiver education, especially for mothers with lower educational levels, to enhance awareness of treatment importance. Strategies such as medication reminders, child-friendly formulations, and counseling to address myths and treatment fatigue can help overcome forgetfulness and refusal to take medication. Additionally, financial support or subsidized treatment programs may assistspective, multicenter, multiethnicity research work including other factors should be done to better understand the association between non families with lower income, ensuring better access to AEDs. Further pro-adherence to AEDs and the risk of seizures.

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