

The prevalence and major determinants of non-compliance with anti-seizure medication among children

Received: 18 Sep. 2021
Accepted: 22 Nov. 2021

Ladan Afsharkhas¹, Shabnam Zamani¹, Azita Tavasoli¹, Babak Zamani², Atefeh Talebi³

¹ Department of Pediatric Neurology, Hazrat-e Ali Asghar Hospital, Iran University of Medical Sciences, Tehran, Iran

² Department of Neurology, Firouzgar Hospital, Iran University of Medical Sciences, Tehran, Iran

³ Colorectal Research Center, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Keywords

Epilepsy; Seizures; Drug Compliance; Anticonvulsants; Child

Abstract

Background: A wide range of adherence to the use of anti-seizure medications has been reported among children with the disease, and accordingly, various factors on the degree of adherence to the drug have been reported. But in our society, there is no clear picture of drug adherence and related factors among children with seizures. We evaluated the frequency of adherence to anti-seizure medication as well as related factors.

Methods: This cross-sectional study was conducted on 120 children with epilepsy who referred to Ali Asghar Hospital in Tehran, Iran, during 2019 and 2020. Along with demographic characteristics, adherence to antiepileptic medications was assessed by the Modified Morisky Scale (MMS).

Results: The overall frequency of adherence to anti-seizure medications among children was reported to

be about 41.7%. Among all baseline characteristics, much higher adherence was revealed in patients with educated parents. The rate of drug adherence in children with a history of perinatal morbidities was much lower than in other patients. The type of seizure could also affect the rate of drug adherence as the highest and the lowest adherence was found concerning focal impaired awareness seizure (57.1%) and atonic seizures (11.1%) indicating a significant difference ($P = 0.022$). The most common causes of non-adherence to treatment were expressing inability to treat the patient (23.0%), parents' forgetfulness to give medicine to the child (18.3%), and not taking medication when traveling or leaving home (16.7%).

Conclusion: The lower level of education of the parents, type of seizure, as well as the presence of

How to cite this article: Afsharkhas L, Zamani S, Tavasoli A, Zamani B, Talebi A. The prevalence and major determinants of non-compliance with anti-seizure medication among children. *Curr J Neurol* 2022; 21(1): 23-8.

underlying perinatal morbidity in the child can predict non-compliance with anticonvulsant medication regimens among affected children.

Introduction

Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and the neurobiological, cognitive, psychological, and social consequences of this condition.

Seizure is caused by abnormal, cortical, and neuronal hyperexcitability and is characterized by abnormal or normal-appearing brain scans.^{1,2} In addition to physical injuries, epilepsy also hurts the patient and the individual, social, and economic aspects of the patient's life. Proper control of epilepsy with the use of anti-seizure medications prevents many side effects.³ The incidence of epileptic seizures is higher in the early years of life and in 42% of cases, seizures occur before the age of 22.⁴ In Iran, the prevalence of epilepsy is estimated at 1.3% of the total population.⁵ Treatment of epilepsy is based on drug therapy, and in recent years, the number of anti-seizure medications approved by the Food and Drug Administration (FDA) has increased dramatically. However, the seizure has been remained uncontrollable with medication in 30% to 35% of patients.⁶ According to the results of studies, the most common cause of recurrence of epileptic seizures is non-compliance with the medication regimen by patients or arbitrary discontinuation of these drugs.⁷ In various texts, several definitions of adherence to the drug regimen have been presented. In a comprehensive definition, "adherence to the medication regimen is the use of prescribed drugs at the correct time and amount, and continuing to use them during the prescribed period". Evidence suggests that non-adherence to the medication regimen is a major problem in patients with chronic diseases such as hypertension (HTN), asthma and other chronic respiratory diseases, diabetes, and epilepsy.⁸ Non-adherence to the medication regimen not only reduces the effects of treatment but also increases the financial burden associated with chronic diseases.^{9,10} Epilepsy is also a chronic disease and non-adherence to the medication regimen is one of the problems in its treatment. It has been determined that 30% to 60% of patients with epilepsy do not adhere to the medication regimen.⁶ The results of studies show that there is a significant relationship between adherence to the drug regimen and control of epileptic seizures as

well as mortality. In one study, the mortality of patients with epilepsy who did not adhere to the medication regimen was three times higher than that of patients with adherence to the medication regimen.¹¹ It should be noted that the degree of adherence to the drug regimen varies in different conditions. In those who have just started treatment and for patients with acute illness for whom long-term use of the drug does not seem necessary, the rate of adherence is high.⁵ It means that the rate of adherence decreases over time, so that after three months, 21% and after one year, 88% of patients stop their medication. Poor adherence to the medication regimen is a serious problem, because almost half of the patients with chronic diseases do not take their prescribed medications.⁷ In one study, one-third of adolescents with epilepsy showed poor adherence to treatment.¹¹ In the social dimension, people with epilepsy may experience social isolation and limitations or may feel unable to work and be rejected by others. All of these factors reduce their level of psychosocial performance, self-efficacy, and quality of life (QOL).¹² Our study was designed to determine the factors affecting drug adherence in patients with epilepsy to identify and eliminate them and help improve the treatment process and QOL of children and adolescents with epilepsy.

Materials and Methods

This cross-sectional study was conducted on 120 children with epilepsy who referred to Ali Asghar Hospital in Tehran, Iran, during 2019 and 2020. Samples were selected by available sampling method, based on inclusion criteria, which were a definite diagnosis of the disease by a neurologist, aged 1 to 15 years, lack of physical and mental disability, literacy, and taking at least one anticonvulsant drug for at least 6 months. The data collection tool consisted of two questionnaires: 1) a questionnaire containing demographic information completed by the samples, which was prepared after studying the texts and articles related to drug adherence and then was released to experts to determine the validity of the content. In addition to demographic characteristics such as age, sex, education, marital status, occupation, etc., possible factors related to drug adherence and the number of seizures in the past 3 months as well as drug side effects were also examined. 2) The Modified Morisky Medication Adherence Scale (MMAS), also known as the Modified Morisky Scale, designed by Morisky

et al. in 1986 to assess drug adherence in different disorders was also used.¹³ This tool includes eight 5-point questions based on the Likert scale, with a score of 0 for never, 1 for rarely, 2 for occasionally, 3 for more often, and 4 for always adherence to drug use. Four terms of this questionnaire include: 1) forgetfulness in taking the drug, 2) carelessness when taking the drug, 3) stopping the drug if there are no seizures, and 4) stop taking the drug due to its side effects. In this questionnaire, the achievable score of each question is rated as 0 to 4. The score range of this questionnaire is 0 to 16, which higher score indicates lower adherence. Content validation and face validity methods were used to determine the validity of data collection tools. After studying several books and articles, the epilepsy self-management behaviors questionnaire and the demographic profile form were available to 10 faculty members of the School of Nursing and Midwifery of Iran University of Medical Sciences, Tehran, 5 neurologists, and 5 patients with epilepsy and then were examined and judged in terms of content validity and formal validity, and according to their comments and suggestions for improvement, the necessary changes were considered. After collecting patients' background information based on a questionnaire containing demographic information, the MMAS questionnaire was provided to patients and their parents, and information related to the degree of adherence to medication regimens was collected.

For statistical analysis, results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t-test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. P-values \leq 0.05 were considered statistically significant. For the statistical analysis, the SPSS statistical software (version 23, IBM Corporation, Armonk, NY, USA) was used.

Results

In the present study, a total of 120 children with seizures admitted to the hospital were included in the study. The mean age of patients was 7.58 ± 4.36 years in the range of 1 to 15 years and 62.5% were boys. Baseline characteristics were summarized in table 1. Most fathers and mothers had a good level of education. In terms of the type of seizure, 29.2% had generalized tonic-clonic seizure, 17.5% had

focal impaired awareness seizure, 15.0% had atonic type, 9.2% had nonmotor type, 16.7% had tonic type, and 12.5% had other types of seizures. In total, in 43 cases (35.8%), there was a family history of seizures, which included 18 cases in the father, 8 cases in the mother, 5 cases in the brother, 7 cases in the sister, and 5 cases in other relatives. History of prenatal disorders was reported in 34 cases (25.3%), including 6 cases of kernicterus, 11 cases of asphyxia, 11 cases of cerebral palsy, and 6 cases of metabolic disorders. Previous history of anticonvulsant medication was also reported in 61.7% of patients. Table 2 presented the antiepileptic medications in use along with dosage and duration of use.

Table 1. Baseline characteristics of study population (n = 120)

Item	Value
Gender (male)	75 (62.5)
Age (year)	7.58 ± 4.36
Father's education level	
Undergraduate	15 (12.5)
Diploma	30 (25.0)
Associate	16 (13.3)
Bachelor	33 (27.5)
Higher	26 (21.6)
Mother's education level	
Undergraduate	23 (19.2)
Diploma	48 (40.0)
Associate	4 (3.3)
Bachelor	23 (19.2)
Higher	22 (18.3)
Type of seizure	
Generalized tonic-clonic	35 (29.2)
Focal impaired awareness	21 (17.5)
Atonic	18 (15.0)
Nonmotor	11 (9.2)
Tonic	20 (16.7)
Other	15 (12.5)
Family history of epilepsy	43 (35.8)
Prenatal problems	34 (25.3)
Previous history of antiepileptic medications	74 (61.7)
Mean time of previous use of anticonvulsant drugs (months)	19.44 ± 13.51

Data are reported as mean \pm standard deviation (SD) or number and percentage

In terms of adherence to prescription drugs, out of a total of 120 patients studied, optimal adherence was observed in 50 cases (41.7%). The most common causes of non-adherence to treatment (Table 3) were expressing inability to treat the patient (23.0%), parents' forgetfulness to give medicine to the child (18.3%), and not taking medication when traveling or leaving home (16.7%).

Table 2. Antiepileptic medications in use along with dosage and duration of use (n = 120)

Drug	n (%)	Dosage (mg)	Time of using (month)
Phenobarbital	50 (41.7)	15 to 60	6 to 48
Carbamazepine	20 (16.7)	100 to 600	6 to 48
Sodium valproate	30 (25.0)	200 to 750	6 to 60
Phenytoin	46 (38.3)	100 to 500	6 to 72
Lamotrigine	23 (19.2)	25 to 100	6 to 48
Levebel	16 (13.3)	250 to 1000	6 to 36
Others	15 (12.5)	10 to 250	6 to 36

As shown in table 4, drug adherence was independent of patients' sex ($P = 0.069$), age ($P = 0.185$), family history of seizure ($P = 0.459$), and type of drugs ($P = 0.468$). However, the adherence to antiepileptic medications was significantly higher in patients with more educated fathers ($P = 0.002$) and mothers ($P = 0.035$), and in those without perinatal morbidities ($P = 0.001$). The type of seizure could also affect the rate of drug adherence as the highest and the lowest adherence was found concerning focal impaired awareness seizures (57.1%) and atonic seizures (11.1%), indicating a significant difference ($P = 0.022$). However, the type of medication did not affect the rate of adherence to medication ($P = 0.468$) (Figure 1).

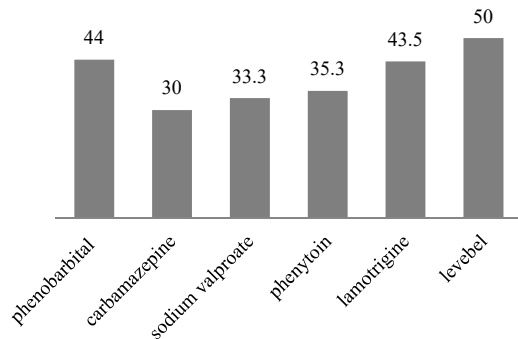


Figure 1. Adherence to medication based on the type of drug used

Discussion

Full adherence to anticonvulsant medication is

critical, especially in affected children. In addition to the complete supervision of the patient's parents on how to prescribe the medication, the patient's desire to receive the medication can also be considered as a factor influencing the implementation of the medication protocol. Based on various studies, a wide range of adherence to the use of anti-seizure medications has been reported among children with the disease, and accordingly, various factors on the degree of adherence to the drug have been reported. But in our society, there is no clear picture of drug adherence and related factors among children with seizures. Therefore, we decided to evaluate the frequency of adherence to anti-seizure medications as well as related factors. In this evaluation, we first showed that the overall frequency of adherence to anti-seizure medications among children was reported to be about 41.7%, which was quite in the middle of the reported range of adherence in other studies. In the study of Yang et al.,¹⁴ the frequency of complete, relative, and poor adherence to anticonvulsant therapy was 21.3%, 51.4%, and 27.3%, respectively. In the study of Shetty et al.,¹⁵ in total, 30.9% of 320 children had adherence to prescribed medications. In the study of Modi et al.,¹⁶ the adherence rate within one month from the start of treatment was 79.4%. In the study of Jacob et al.,¹⁷ adherence to anti-seizure medications was 68.9%. In a systematic review study by Yang et al.,¹⁸ the rate of drug adherence was estimated to be between 22.1% and 96.5%, with an overall average of 55%.

Table 3. The most common causes of non-adherence to treatment expressed by parents

Reason	n (%)
Parents' forgetfulness to give medicine to the child	22 (18.3)
Not giving medication for the last two weeks for reasons other than forgetfulness	14 (11.7)
Not giving medicine due to the deterioration of the patient's general condition without consulting a doctor	3 (2.5)
Not taking medication with you when traveling or leaving home	20 (16.7)
Not giving medication to the child the day before	8 (6.7)
Not giving medicine due to the improvement of the patient's general condition without consulting a doctor	3 (2.5)
Expressing inability to treat the patient	28 (23.3)
Inability and difficulty in remembering the necessary medications prescribed	13 (10.8)

Table 4. Adherence to medication according to baseline parameters

Item	Adherence rate (%)	P
Gender		0.069
Male	48.0	
Female	31.1	
Father's education level		0.002
Undergraduate	13.3	
Diploma	16.7	
Associate	25.0	
Bachelor	48.5	
Higher	53.8	
Mother's education level		0.035
Undergraduate	26.1	
Diploma	37.5	
Associate	50.0	
Bachelor	43.5	
Higher	63.6	
Type of seizure		0.022
Generalized tonic-clonic	45.7	
Complex partial	57.1	
Atonic	11.1	
Absence	18.2	
Tonic	50.0	
Other	53.3	
Family history of seizure		0.459
Positive	37.2	
Negative	44.2	
Prenatal problems		0.001
Positive	17.6	
Negative	51.2	

Moreover, in the study of Nazziwa et al.,¹⁹ adherence to anti-seizure medications was estimated to be 79.5%. Finally, in the study of Lee et al.,²⁰ adherence to anticonvulsant therapy during the first year was 70.1%, which was reduced to 56.8% in the second year. Therefore, a review of different studies showed a very diverse degree of adherence to the treatment of children with seizures with anti-seizure medications, that can predict the involvement of a wide range of different factors, especially demographic characteristics.

In the second step, to justify such a significant difference in the frequency of drug adherence, we also evaluated the features associated with this adherence therapy and showed that among all baseline characteristics, firstly, much higher adherence was revealed in patients with educated parents. It could be said that, the level of awareness of educated parents about the importance of medication in epileptic patients and also the degree of their responsibility to follow the disease was higher than parents with a lower social levels. As a second finding, the rate of drug adherence in children with a history of perinatal morbidities

was much lower than in other patients. In other words, it seems that the main reason for the decrease in drug adherence among children with a history of perinatal morbidities, fearful parents from worsening the clinical condition of their children with anti-seizure medications and also fear from severe side effects in these children after taking drugs. In contrast, other factors including gender, age, family history of seizures, previous history of anticonvulsant drug use, and type of anticonvulsant drug did not affect drug adherence in these patients. Comparison of the findings of this study with other studies indicates the similarity of our findings with previous studies. In the study of Yang et al.,¹⁴ patient age, type of seizure, total family income, and source of drug information were identified as factors related to adherence therapy, which, of course, differed significantly from the findings of our study. In the study of Shetty et al.,¹⁵ there was no relationship between the degree of adherence therapy with clinical features such as gender, duration of seizure period, other underlying clinical problems, and seizure frequency. In the study of Modi et al.,¹⁶ adherence therapy depended only on the socioeconomic level of individuals and was not affected by gender, age, type of seizure, type of prescription drug, frequency of seizures, or duration of seizure onset, which is quite similar to our study. In the study of Jacob et al.,¹⁷ in terms of drug adherence than children in East Germany (in West Germany, the socioeconomic level of individuals is much higher than in East Germany), but the degree of adherence was not related to the type of drug used. In a systematic review study by Yang et al.,¹⁸ family financial support, family size, support of health care institutions, and higher socioeconomic status were identified as factors affecting compliance. In this study, it was also shown that the results regarding the effect of age, frequency of seizures, type of seizure, type of drug, and the number of prescribed drugs were completely contradictory. In the study by Nazziwa et al.,¹⁹ cases of non-compliance were significantly lower among children whose parents were employed.²⁰ Besides, in the study by Lee et al.,²⁰ patients who started treatment before the age of one year, patients who received treatment with older generations of patients, or those who had localized seizures were much less likely to follow treatment. Overall, about the factors related to the lack of drug adherence among children with seizures, what can be emphasized and seems

certain is the reduction of drug adherence in families with lower social and economic levels is accompanied with a low level of awareness about the importance of this obedience. Therefore, increasing the awareness of these families can lead to increased treatment adherence in such families.

Conclusion

As a final result, first, the frequency of non-adherence to the medication regimen among children with seizures is estimated at 41.7%. The lower level of education of the parents, type of seizure, as well as the presence of underlying

perinatal morbidities in the child will predict non-compliance with anticonvulsant medication regimens, while gender, age, family history of seizures, history of taking anti-seizure medications, or type of prescription drugs will not affect this drug adherence.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: A practical clinical definition of epilepsy. *Epilepsia* 2014; 55(4): 475-82.
2. Ito H. What should we do to improve patients' adherence? *J Exp Clin Med* 2013; 5(4): 127-30.
3. Baker GA, Jacoby A, Gorry J, Doughty J, Ellina V. Quality of life of people with epilepsy in Iran, the Gulf, and Near East. *Epilepsia* 2005; 46(1): 132-40.
4. Asadi-Pooya AA. Drug compliance of children and adolescents with epilepsy. *Seizure* 2005; 14(6): 393-5.
5. Ashktorab T, Yadollahi S, Safavi Bayat Z, Zayery F. The correlation between self-management behaviors and drug adherence among people with epilepsy in Iran. *Epilepsy Association*. *Avicenna J Nurs Midwifery Care* 2013; 21(2): 5-15. [In Persian].
6. O'Brien MK, Petric K, Raeburn J. Adherence to medication regimens: Updating a complex medical issue. *Med Care Rev* 1992; 49(4): 435-54.
7. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. *J Clin Epidemiol* 2001; 54(Suppl 1): S57-S60.
8. Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. *Epilepsia* 2008; 49(3): 446-54.
9. Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: Findings from the RANSOM Study. *Neurology* 2008; 71(20): 1572-8.
10. Kazemi Majd R, Hosseini M, Safi MH, Norouzi K, Hosseinzadeh S. The effect of self-care education based on short message service on self-efficacy and adherence to the medication regimen in adolescents with epilepsy referred to Iran Epilepsy Association in 2016. *J Nurs Edu* 2017; 6(4): 48-55. [In Persian].
11. Yadegary MA, Dehghan-Naeyeri N, Aliasgharpoor M, Naseh L. The effect of educational program on drugs self-management in patient with epilepsy- A randomized clinical trial. *J Clin Nurs Midwifery* 2013; 2(3): 86-94. [In Persian].
12. Al-Qasem A, Smith F, Clifford S. Adherence to medication among chronic patients in Middle Eastern countries: Review of studies. *East Mediterr Health J* 2011; 17(4): 356-63.
13. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; 24(1): 67-74.
14. Yang C, Yu D, Li J, Zhang L. Prevalence of medication adherence and factors influencing adherence to antiepileptic drugs in children with epilepsy from western China: A cross-sectional survey. *Epilepsy Behav* 2020; 104(Pt A): 106662.
15. Shetty J, Greene SA, Mesalles-Naranjo O, Kirkpatrick M. Adherence to antiepileptic drugs in children with epilepsy in a Scottish population cohort. *Dev Med Child Neurol* 2016; 58(5): 469-74.
16. Modi AC, Morita DA, Glauser TA. One-month adherence in children with new-onset epilepsy: white-coat compliance does not occur. *Pediatrics* 2008; 121(4): e961-e966.
17. Jacob L, Hamer HM, Kostev K. Adherence to antiepileptic drugs in children and adolescents: A retrospective study in primary care settings in Germany. *Epilepsy Behav* 2017; 75: 36-41.
18. Yang C, Hao Z, Yu D, Xu Q, Zhang L. The prevalence rates of medication adherence and factors influencing adherence to antiepileptic drugs in children with epilepsy: A systematic review and meta analysis. *Epilepsy Res* 2018; 142: 88-99.
19. Nazziwa R, Mwesige AK, Obua C, Ssenkusu JM, Mworosi E. Adherence to antiepileptic drugs among children attending a tertiary health unit in a low resource setting. *Pan Afr Med J* 2014; 17: 44.
20. Lee YK, Ah YM, Choi YJ, Cho YS, Kim KJ, Lee JY. Antiepileptic drug adherence and persistence in children with epilepsy attending a large tertiary care children's hospital. *Epileptic Disord* 2016; 18(4): 408-17.