Original article

Adherence to Anti-seizure Drugs and Associated Factors among Children with Epilepsy in central Sudan

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Abstract:

Background: Epilepsies are the most common neurological disorder in children worldwide. They result in disability or even death. Adherence to anti-seizure drugs (ASDs) is challenging for children with epilepsies.

Methods: This cross-sectional descriptive study was conducted on 67 children with epilepsies age between (2-16 years of age) on follow up visits at neurology refer clinic at Wad Medani Pediatric Teaching Hospital; Central Sudan from February to July. 2022. Adherence to ASDs was measured using Morisky's Medication Adherence Scale eight – items (MMAS-8) translated to the local language. Descriptive analysis was conducted to calculate frequencies and percentages for categorical data, chi-square test for associated factors with adherence. A P-value of < 0.05 was considered statistically significant.

Results: Gender analysis showed that 36 (53.7%) of patients were males. Forty-eight (71.6%) had good adherence to their medications. Thirty-three (49.3%) had 1-12 seizures/year. Thirty-nine (58.2%) of participants had generalized seizures while 22 (32.8%) had focal seizures. Sixty-six (95.5%) of study patients on poly therapy had good adherences. Adherence was not found to be associated with sex, age, parental education, employment status, ASDs, duration of epilepsy, type of epilepsy, seizures frequency or monotherapy versus poly therapy (p value > 0.05).

Keywords: Anti-seizure drugs, Adherence, Epilepsies, children, Sudan.

1. Introduction

Epilepsy is the most common neurological disorder in children. In Sudan epilepsy accounts for 1.6 annual mortality rates and 238.7 disability adjusted life years per 100 000 (1). Treatment of epilepsy with anti-seizure drugs (ASDs) for 2-5years is important to control convulsions, this requires good adherence to the medications (2). Medical adherence is generally defined as "the extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider" (3). Adherence to ASDs is challenging for epileptic children (4).

Studies in children with epilepsy have reported adherence in 50–96.5% (3) and (5). Accurate assessment of adherence behavior is necessary for effective and efficient treatment

planning, and for ensuring that changes in health outcomes can be attributed to the recommended regimen (6)

2. Materials and Methods

Study Design:

Cross-sectional descriptive, hospital-based study design was used for the assessment of adherence of patients/ family members to ASDs

Study Area:

This study was conducted at Wad-Medani Pediatric Teaching Hospital; a tertiary hospital in Wad-Medani city the capital of Gezira State in Central Sudan. The patients and their families visit the outpatient refer clinic every month for regular follow up where the study was done. The study was conducted in the period from February/2022 to July/ 2022.

Study Population:

The subjects of the study were children with epilepsy (2–16 years) who had been visiting neurology refer clinic and their care givers. Total number of study sample was 67. Probability sampling (systematic random sampling) was used.

Inclusion criteria:

Children who received an epilepsy diagnosis and were prescribed one or more ASD/s; children age between 2 and 16 years; had no comorbid medical conditions requiring a daily medication, had no significant developmental disorders reported by their caregivers, and informed consent provided by the patient or family members. Exclusion criteria were refused consent and any criterion not included in inclusion criteria.

Data Collection method:

A patient was assigned an identification number, and then interview was done to older patients directly or to the care givers of younger patients who could not respond to the interview. Descriptive medical data (type of epilepsy, disease duration, prescribed ASDs, and seizure frequency) and demographic data (child age and gender) were collected from patient's card. Father employment status was collected directly from the family member during the interview.

Seizures were classified according to the International League Against Epilepsy classification (ILAE) (7)

Patients and/or caregivers were interviewed using eight-item Morisky Medication Adherence Scale (MMAS-8) sheet to assess the adherence to the ASD/s. MMAS-8 was translated to Arabic language to suit Sudanese patients/ caregivers (**Appendix A**). Each item was scored as either 0 (Yes) or 1 (No). The score of each item was then summed up to give a range of scores from 0 to 8. A score of >6–8 suggested that the patient had good adherence, while a score of ≤ 6 suggested that the patient had poor adherence.

Statistical analysis:

Collected data was entered into the statistical package of social sciences (SPSS) version 20 and descriptive analysis was conducted to calculate frequencies and percentages for categorical data, chi-square test for association. A P-value of < 0.05 was considered statistically significant in related tests.

3. Results

3.1. Socio-clinic demographic data:

Total number of patients/family members who were studied was 67. There were 36 (53.7%) of study patients were males and 31(46.3%) were females. There were 27 (40.3%) of patients were in age between 2-6 years, and 19 (28.4%) were between 12-16 years old. Exactly 64S (95.5%) of participants had their fathers employed. There were 33 (49.3%) of study

patients had 1-12 seizures/year, 18 (26.9%) were Seizure free for > 12 months, 10 (14.9%) had 2-4 seizures/month, 3 (4.5%) of had 1-7 seizures/ week, and 3 (4.5%) had daily seizures. There were 39 (58.2%) of participants had generalized seizures, 22 (32.8%) had focal seizures, 5 (7.5%) had myoclonic seizures, and 1 (1.5%) had unclassified seizures. Twenty-nine (43.5%) of study patients were prescribed sodium valproate, 18 (27%) were prescribed carbamazepine-IR, 7 (10.5%) were prescribed carbamazepine-CR, 6(9%) were prescribed levetiracetam and

the rest were prescribed polytherapy involved clonazepam as add on therapy. Exactly (76.1%) of study patients had seizure duration for > one year, 7 (10.4%) of study patients had duration of 5-8 months. Sixty (89.6%) of study patients were prescribed monotherapy. Table (1)

Table 1. This is a table of distribution of Study patients according to clinical demographic characteristics

Variable	Frequency	Percent %
Seizure frequency		
Seizure free for > 12 months	18	26.9%
1-12 seizures/ year	33	49.3%
2-4 seizures/ month	10	14.9%
1-7seizures / week	3	4.5%
Daily seizures	3	4.5%
Type of epilepsy		
Generalized	39	58.2%
Focal	22	32.8%
Myoclonic	5	7.5%
Not classified	1	1.5%
Prescribed ASDs		
Valproate	29	43.3%
Carbamazepine	25	37.3
Levetiracetam	6	9%
Other ASDs	7	10.4%
Duration of epilepsy		
1-4 months	4	6%
5-8 months	7	10.4%

9-12 months	5	7.5%
> One year	51	76.1%
Other		
Monotherapy	60	89.6%
Polytherapy	7	10.4%
Total		
	67	100%

3.2. Adherence to ASDs:

There were 48 (71.6%) of study patients had good adherence to ASDs, and 19 (28.4%) of patients had poor adherence to ASDs. Figure 1.
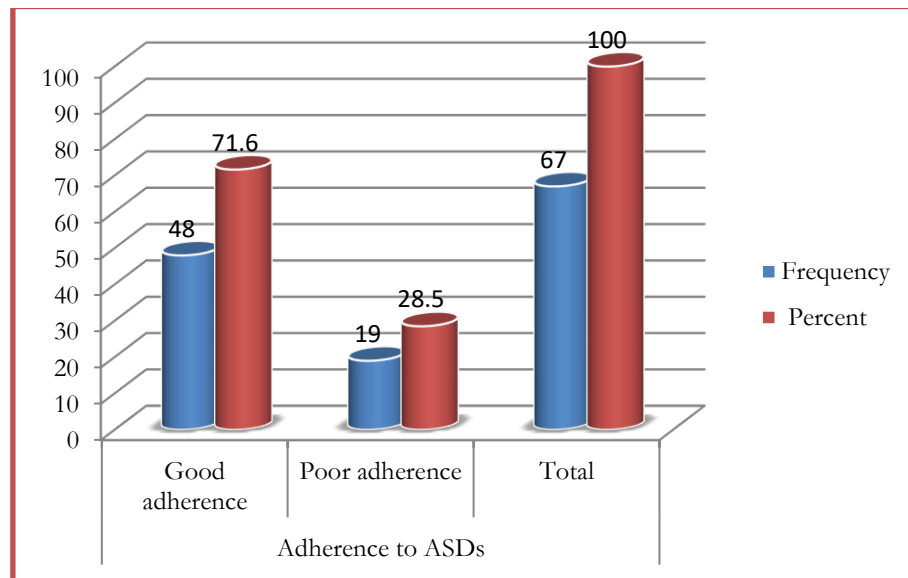

Figure 1. This is a figure of distribution of patients according to adherence to ASDs

3.3. Causes of poor adherence to ASDs:

There were 16 (23.9%) of factors were "forgot to take their ASDs", and 9 (13.4%) of causes were "did not take ASDs to cause other than forgetfulness". Table 2

Table 2. This is a table of distribution of patients according to causes of poor adherence

		Frequency	**Percent**
Causes of poor adher-ence	Forgot to take ASDs	16	23.9
	Did not take ASDs	9	13.4
	Cut back or stopped ASDs when felt worse	5	7.5

	did not take ASDs yesterday	1	1.5
	Felt hassled about sticking to ASDs plan	5	7.5
	Stopped ASDs when felt better	4	6.0
	How often had difficulty remember- ing to take ASDs(sometimes, usually, all the time)	5	7.5
	Total	45	67.2
	System	22	32.8
Total		67	100.0

3.4. Duration of epilepsy and adherence to ASDs:

There were 4 (57.1%) of the study patients with duration of 5-8 months had poor ad-herence, 4 (80.0%) , 3(75.0%) and 38 (74.5%) of the study patients with duration of 9-12 months, 1-4 months and > one year respectively had good adherence to ASDs. Table 3.

Table 3. This is a table of distribution of study patients according to adherence to ASDs and duration of epilepsy

Adherence to ASDs drug/s * Duration of epilepsy Crosstabulation							
			Duration of epilepsy				Total
			1-4 months	5-8 months	9-12 months	> one year	
Adherence to ASDs drug/s	Good ad-herence	Count	3	3	4	38	48
		% within Duration of epi-lepsy	75.0%	42.9%	80.0%	74.5%	71.6%
	Poor ad-herence	Count	1	4	1	13	19
		% within Duration of epi-lepsy	25.0%	57.1%	20.0%	25.5%	28.4%
Total		Count	4	7	5	51	67
		% within Duration of epi-lepsy	100.0%	100.0%	100.0%	100.0%	100.0%

3.5. Monotherapy versus polytherapy and adherence to ASDs:

There were 18 (30%) of study patients who received monotherapy had poor adherence and 6(85.7%) of study patients who were prescribed polytherapy had good adherence. Table 4.

Table 4 This is a table of distribution of study patients according to adherence to ASDs and mono-therapy versus polytherapy

Adherence to ASDs drug/s * Monotherapy versus polytherapy Crosstabulation					
			Monotherapy versus polytherapy		Total
			Monotherapy	Polytherapy	
Adherence to ASDs drug/s	Good adherence	Count	42	6	48
		% within Monotherapy versus polytherapy	70.0%	85.7%	71.6%
	Poor adherence	Count	18	1	19
		% within Monotherapy versus polytherapy	30.0%	14.3%	28.4%
Total		Count	60	7	67
		% within Monotherapy versus polytherapy	100.0%	100.0%	100.0%

3.6. Association tests for adherence (Chi-square test):

Adherence was not found to be associated with sex, age, parental education, employment status, ASDs, duration of epilepsy, type of epilepsy, seizures frequency, monotherapy or polytherapy (p-value > 0.05). Table 5

Table 5. This is a table of Chi-square test for association of socio-clinical variables and adherence

Variable	Pearson chi-square test		
	Value	df	Asymp.sig.(2-sided) (p-value)
Sex	0.432	2	0.511*
Age	2.06	1	0.357*
Parental education	2.92	3	0.404*
Employment status	1.24	1	0.265*
ASDs	7.07	8	0.528*
Duration of epilepsy	3.255	1	0.354*
Type of epilepsy	4.63	3	0.201*
Seizures frequency	2.857	4	0.582*

Monotherapy versus polytherapy	0.762	1	0.383*

4. Discussion

More than half of the study patients were males. That means epilepsy was more common in males than in females in our setting. This result agreed with a result from a study by (8) which showed male predominance (64.9%) and study conducted in Southwest Ethiopia (54.7%) (9).

Epilepsy was more common in young children than in older children in our setting. This result agreed with fact that the resolution of epilepsy occurs spontaneously when the brain develops with age advancing. Around half of the study patients had 1-12 seizures / year.

More than half of study patients were diagnosed with generalized seizures which were the most common type of epilepsy stated by a study (10). Another study from Sweden found that focal seizures alone or plus generalized seizures were more common (54.0%) (11). Focal epilepsy was also common in our setting but with fewer frequencies.

Near to three quarter of study patients had good adherence to their medications. This result is relatively good for poor setting like ours. Similar results of adherence (68.9%) was found in a study conducted in a developed country like Germany (12), and near to a result from a developing country like Uganda(79.5%) (13), but not similar to a result from a study conducted at Nigeria (44.8%) (14).

Valproate as ASD was the most commonly prescribed, followed by carbamazepine. Similar result was found by many studies, (15) from China and (50.5%) from Jordon (16). Levetiracetam as monotherapy was prescribed to a less extent despite that it is one of the safest ASD and involved in management of different types of epilepsy by international guidelines. In our setting; levetiracetam was not available as free.

General adherence was good in around three quarter of study patients. This result was better than the expected when taking in consideration the period during which the study was conducted (Covid-19 pandemic and the Sudanese revolution). Most of the causes for poor adherence stated by the patients/ family members were "forgot to take ASDs" and to less extent "did not take their medications to causes other than forgot". The later cause may be explained in our setting by financial problems that face the majority of the patients' care givers. Sometimes the patients and their family members come from far villages for follow up and for filling their prescriptions, this costs them money. Some ASDs specially syrups (like valproic acid and levetiracetam) are expensive and could not be afforded by the patients' care givers, and sometimes could be unavailable at all.

Small number of study patients and family members stated that they had no idea that ASDs should be taken regularly for long time to control seizures. This point should be explained clearly in the future by the health- care giver during counseling.

About three quarter of patients who were on valproate had a good adherence to it, most of patients who were prescribed CBZ had better adherence to controlled release CBZ than to immediate release CBZ. This may be due to better tolerability of controlled release form.

Most of the study patients were on monotherapy. Those who were on polytherapy had the higher percentage of adherence despite that other research found it to be of low percentage because of poor compliance (17, 18), The number of study patients who were prescribed polytherapy was small and therefore cannot be used to judge that adherence was better in this category of study patients.

Quarter or near to quarter of the study patients had poor adherence to ASDs. This was observed in different categories of epilepsy durations. Nonetheless, those with duration of

the disease (5-8) months, the adherence were poor in more than 50%. This result may be affected by the small number of study patients in this category.

Adherence was not found to be associated with any factors in our study. Other studies found it to be associated with age of patient, type of epilepsy, total household income, and source of drug information (5), age, the frequency of seizure, type of seizures, type of medication and the number of administered drug (4) presence of seizure attack in the past 3months and low family income (10)

5. Conclusions

Adherence to anti-seizure drugs was not as good as required. This study assessed adherence by subjective method, objective method is further needed to assess adherence to ASDs however. More efforts are needed to provide patients and their families with information about the importance of adherence to their medications, and to duration the government to supply the medications for free to patients.

6. Patents

Author Contributions: Conceptualization, investigation, methodology: Prof. Imad-Eldeen Mohammed Taj El, Prof. Haydar El Hady Babikir, and Dr. Ibrahim Osman M. Omer. Data curation, software, formal analysis, writing original draft and visualization: Dr. Salma Hassan Mohammed Eltahir. Resources (Patients): Prof. Haydar El Hady Babikir and Dr. Salma Hassan Mohammed Eltahir. Validation: Prof. ImadEldeen Mohammed Taj El Deen and Prof. Haydar El Hady Babikir. Writing-review and editing: Prof. ImadEldeen Mohammed Taj El Deen and Prof. Haydar El Hady Babikir.

Institutional Review Board Statement: This study was conducted after it had been approved by the Ministry of Health Gezira state and Ethical Committee of University of Gezira before patients had been approached, recruited, and enrolled in the study. This article was a part of another study carried out by the same authors. So, ethical approval was taken for the whole study and it possessed the number: 5-22 on 22/2/2022; however, this article involved no experimental tests on humans or animals.

Informed Consent Statement: "Informed consent was obtained from all subjects involved in the study."

Conflicts of Interest: "The authors declare no conflict of interest."

Appendix A

Arabic translated form of eight- item Moriskey Medication Adherence scale (MMAS-8)

	Yes نعم (0)	No لا (1)
1-do you sometimes forget to take medication? هل تنسى احيانا اخذ / اعطاء الدواء لطفلك؟		
2-people sometimes miss taking medications for reasons other than forgetting. Over the past 2 weeks, were there any days when you did not take your medication? **لايتناول الناس احيانا الدواء لاسباب اخرى غير النسيان. هل حدث في الاسبوعين الماضيين انك لم تاخذ / لم تعط طفلك الدواء في بعض الايام ؟**		
3-have you ever cut back or stopped taking medication without telling your doctor because you felt some worse when you took it? **هل حدث وان توقفت عن اخذ / اعطاء الدواء لطفلك بدون اخبار طبيبك بسبب الشعور بحال اسوء عند تناول الدواء؟**		
4-When you travel or leave home, do you sometimes forgot to bring up your medication? **هل تنسى احيانا اخذ دوائك/ دواء طفلك معك عندما تسافر او تغادر المنزل ؟**		
5-did you take all your medication yesterday? **هل اخذت كل ادويتك/ اعطيت طفلك كل ادويته بالامس؟**		
6-when you feel like your symptoms are under control, do you sometimes stop taking your medication? **هل تتوقف عن تناول ادويتك /عن اعطاء طفلك ادويته عندما تحس باختفاء اعراض المرض؟**		

7-taking medication every day is a real inconvenience for some patients.do you ever feel hassled about sticking to your medication plan? اخذ الدواء يوميا يعتبر مصدر ازعاج حقيقي لبعض الناس. هل شعرت يوما بالضيق حيال خطة العلاج ؟		
8-how often have you difficulty remembering to take all your medication? كم عدد المرات التي وجدت فيها صعوبة في تناول /اعطاء الدواء لطفلك؟ Never /rarely………………………………. ابدا/ نادرا …………… Once in a while ……………………………… مرة كل حين ………… Sometimes ……………………………….. في بعض الاحيان …………… Usually ……………………………………… عادة………… All the times ………………………………… كل الوقت…………		
Score (0-8) درجة (0-8)		
Good Adherence(> 6-8)/ pooradherence (≤ 6)		

References

1. Bashir MBA, Cumber SN. The quality of life and inequalities in health services for epilepsy treatment among patience in the urban cities of Sudan. The Pan African Medical Journal. 2019;33.
2. Katabalo DM, Nyamu DG, Amugune B, Karimi PN, Okalebo FA, Bosire KO, et al. Determinants of adherence to anticonvulsants therapy among outpatient epileptic children in a Kenyan Referral Hospital. African Journal of Pharmacology and Therapeutics. 2015;4(2).
3. Shetty J, Greene SA, Mesalles-Naranjo O, Kirkpatrick M. Adherence to antiepileptic drugs in children with epilepsy in a Scottish population cohort. Developmental Medicine & Child Neurology. 2016;58(5):469-74.
4. 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 research. 2018;142:88-99.
5. 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 & Behavior. 2020;104:106662.

6. Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia. 2009;50(3):501-9.

7. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522-30.

8. 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 Disorders. 2016;18(4):408-17.

9. Mohammed H, Lemnuro K, Mekonnen T, Melaku T. Adherence to anti-seizure medications and associated factors among children with epilepsy at tertiary Hospital in Southwest Ethiopia: a cross-sectional study. BMC neurology. 2022;22(1):310.

10. Dima SA, Shibeshi MS. Antiepileptic drug adherence in children in southern Ethiopia: a cross sectional study. Plos one. 2022;17(2):e0263821.

11. Larsson K, Eeg-Olofsson O. A population based study of epilepsy in children from a Swedish county. European Journal of Paediatric Neurology. 2006;10(3):107-13.

12. Jacob L, Hamer HM, Kostev K. Adherence to antiepileptic drugs in children and adolescents: A retrospective study in primary care settings in Germany. Epilepsy & Behavior. 2017;75:36-41.

13. Nazziwa R, Mwesige AK, Obua C, Ssenkusu JM, Mworozi E. Adherence to antiepileptic drugs among children attending a tertiary health unit in a low resource setting. Pan African Medical Journal. 2014;17(1).

14. Ejeliogu E, Courage A. Prevalence and factors associated with non-adherence to antiepileptic drugs among children with epilepsy in Jos, Nigeria. Nigerian Journal of Paediatrics. 2020;47(3):240-5.

15. Kwong KL, Tsui KW, Wu SP, Yung A, Yau E, Eva F, et al. Utilization of antiepileptic drugs in Hong Kong children. Pediatric neurology. 2012;46(5):281-6.

16. Albsoul-Younes A, Gharaibeh L, Murtaja AA, Masri A, Alabbadi I, Al-Qudah AA. Patterns of antiepileptic drugs use in epileptic pediatric patients in Jordan. Neurosciences Journal. 2016;21(3):264-7.

17. Shetty J, Kirkpatrick M, Greene S. Adherence to anti-epileptic medication in children with epilepsy from a Scottish population cohort. Archives of Disease in Childhood. 2012;97(Suppl 1):A135-A.

18. Kumar S, Sarangi SC, Tripathi M, Gupta YK. Evaluation of adverse drug reaction profile of antiepileptic drugs in persons with epilepsy: a cross-sectional study. Epilepsy & Behavior. 2020;105:106947.