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Risk factors for seizure recurrence after initial withdrawal of anti-seizure medications in children with epilepsy at Aga Khan University Hospital, Nairobi, Kenya.

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ABSTRACT

Objectives: We sought to determine risk factors associated with seizure recurrence following initial withdrawal of anti-seizure medications (ASM) among children with epilepsy.
Methods: This was a retrospective observational study of children aged between 2 and 18 years with a diagnosis of epilepsy who underwent withdrawal of anti-seizure medication following remission of seizures. All eligible medical records between January 2011 and December 2019 were included. Demographic, clinical, imaging and electroencephalography data of all eligible patients were analyzed against seizure remission within 24 months after withdrawal of ASM, using appropriate parametric and non-parametric tests.
Results: A total of 49 records of children who underwent withdrawal of ASM out of a total of 613 patients on follow up during the same period were included. The median age at ASM withdrawal was 70 months (IQR 52–112 months) and 14 (28.6%) were female. Thirteen patients (26.5%) had seizure recurrence within 24 months following withdrawal of ASM. Focal onset seizure type was associated with significant risk of seizure recurrence (OR 13.7; 95% CI 0.97, 193.54; P value = 0.011). Age at epilepsy diagnosis, abnormal EEG at initiation of treatment and at the time of de-escalation, abnormal MRI findings, first or second degree relative with epilepsy, history of developmental delay, seizure burden, use of 2 or more ASMs and duration of seizure-freedom before de-escalation of ASM were not associated with increased risk of relapse.
Conclusion: Focal onset seizure type is associated with increased with risk of seizure recurrence in this cohort.

Introduction

Successful withdrawal of anti-seizure medications can be achieved in up to 70% of children with controlled epilepsy [1]. Seizure relapse rate of 20–46% have been reported among children and adults undergoing de-escalation of ASM across various studies [2–6].

In a retrospective study of patients aged up to 16 years with idiopathic generalized epilepsy (IGE) followed for at least two years after ASM withdrawal, 54.5% of the seizure relapses occurred within the first six months, 63.6% within 12 months, 81.8% within 18 months and 95.4% after 24 months after withdrawal [7]. Twenty percent of seizure relapses occurred during treatment de-escalation [7]. Mental retardation, history of febrile convulsions, cumulative number of ASM before remission, abnormal first EEG, need for more than one ASM for seizure control and a history of status epilepticus were found to be significantly associated increased risk of seizure recurrence among children following ASM withdrawal [1–5,7].

In a systematic review and individual participant data analysis of 1769 patients, epilepsy duration before remission, seizure-free interval before withdrawal of ASM, age at onset of epilepsy, history of febrile seizures, number of seizures before remission and absence of self-limiting epilepsy syndromes were identified as risk factors for seizure recurrence [2]. A seizure free period of less than two years has been reported to be an independent predictor of increased seizure recurrence [5,8,9].

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In a recent retrospective review of 133 Italian patients aged between 0.8 and 33 years, 45% relapsed and 55% remained seizure-free following withdrawal of ASM [6]. The cumulative risk of seizure recurrence was 13.5% at 6 months, 30.8% at one year and 39.1% at two years. The median time to seizure recurrence from the beginning of ASM tapering was 304 days [6]. Majority of the patients who had seizure recurrence (86.7%), had this occurring within two years.

There is paucity of data on success of ASM withdrawal and risk factors for seizure recurrence in Sub-Saharan Africa (SSA) [10]. The experience is likely to be different from other settings on account of expanded aetiological profile that includes infectious diseases, adverse perinatal outcomes and trauma. In Kenya, the prevalence of epilepsy has been estimated to be 4.0 per 1000 in rural areas with 50.6% of those with Epilepsy being less than 20 years old [11]. The incidence rate of epilepsy is estimated to be 77 per 100,000 person-years of follow-up with 54.5% of those affected being under 20 years of age [12]. The greater prevalence of epilepsy in SSA is likely attributable to greater occurrence of communicable diseases and perinatal brain insults [13]. The greater burden of epilepsy against limited service capacity may mean that relatively fewer children living with epilepsy are considered for ASM withdrawal or a significant proportion of patients access ASM inconsistently making for poorer outcomes and little opportunities for consideration for withdrawal of ASM. We report on our experience with ASM withdrawal at a paediatric neurology service at a tertiary institution in SSA, examining the success rates and the factors associated with seizure recurrence in children with epilepsy following withdrawal of ASM.

Methods

We conducted a retrospective observational study to determine the rate of successful withdrawal of ASM in children with epilepsy and factors associated with seizure recurrence following ASM withdrawal. We conducted the study at Aga Khan University Hospital, Nairobi in Kenya between March 2021 and February 2022. We reviewed all medical records of children seen at the paediatric neurology clinic between 2011 and 2019 to identify patients who were eligible for the study. We recruited children with a clinical diagnosis of epilepsy who were aged between 2 years and 18 years at the time of ASM withdrawal. The decision to withdraw ASM was individualized and was entirely at the discretion of the attending neurologists at the time, in consultation with the patients' families following adequate seizure control. We excluded children who were unreachable for telephone interview to ascertain outcomes after at least 24 months since initial de-escalation of ASM. We obtained demographic and clinical information from the patients' medical records using a structured and coded data collection tool. Telephone interviews were conducted for all patients who were not on active care to determine their clinical progression following initial de-escalation of ASM for a period of at least 24 months.

Successful ASM withdrawal was defined as confirmed absence of seizures for a period of 24 months from the date of initial treatment de-escalation.

Seizure relapse was defined as occurrence of any seizure activity observed clinically at any time following commencement of ASM withdrawal.

De-identified data were verified and entered into a password secured KoBoToolbox® application database in a password secured device. KoboToolbox® is a free and open source platform for collection, management and visualization of data (Kobo Inc. https://www.kobotoolbox.org/).

The data were analyzed using Intercooled STATA Statistical software (College Station, Texas 77845 USA).

We analyzed the proportions of children who remained seizure free following ASM de-escalation, after 6, 12, and 24 months. We applied chi Square test to examine association between categorical variables. Student T-test was used to compare normally distributed continuous data and Wilcoxon Rank sum was applied for non-normal data. Statistical significance was set at 5%. Univariable and multivariable analyses were undertaken to determine factors independently associated with successful ASM withdrawal. Variables of interest included: age, biological sex, age at diagnosis of epilepsy, family history of epilepsy, presence or absence of developmental delay, seizure type or epilepsy syndrome, comorbidities including initial and repeat EEG findings before de-escalation, MRI brain findings, duration of seizure-free period before treatment de-escalation, history of ASM use, seizure type and frequency, timing of seizure recurrence and re-initiation of ASM following seizure recurrence.

Ethical considerations

Permission to review patient records was obtained from The Scientific and Ethics committee of the Aga Khan University Hospital, approval number 2020IERC-145. Data collected were de-identified, coded and stored in a secured data base. For patients who were not on active follow up, a structured document to obtain verbal consent was read out at the commencement of the interview then verbal telephonic consent was obtained from the parent/guardian before obtaining the requisite information related to the study. The interviewer also requested the study participant for permission to record the telephone conversation. An approved phone script prepared in advance was used to guide the brief interview on the two-year outcome for this group of subjects.

Results

We reviewed 613 medical records of patients seen between 2011 and 2019 at the paediatric neurology clinic and identified 49 children who were considered for withdrawal of ASM following seizure remission. The ASM de-escalation period ranged from 6 to 12 weeks. The median age at epilepsy diagnosis was 36 months (IQR 12–72 months) and the median age at ASM withdrawal was 70 months (IQR 52–112 months). Fourteen of the patients (28.6%) were female.

Twelve out of 48 (25%) patients had developmental delay. Brain imaging was available for 39 patients out of which 9 (23.1%) were reported to have structural abnormalities. Twenty-eight of 47 EEGs recorded (59.6%) at presentation were abnormal. Majority of these patients (79.6%) had generalized onset seizures, 8.2% had focal onset and 12.2% had seizure types that were either unclassified or of unknown onset. Thirty-eight patients underwent EEG before de-escalation of ASM. Twenty-four of these children (63%) had normal EEG recordings.

Thirty-six (73.5%) patients remained seizure-free for at least 24 months after the initial de-escalation of ASM while 13 (26.5%) experienced seizure recurrence. The median duration of remission before the initial de-escalation of ASM was 24 months (IQR 20–25 months). The shortest duration of remission to de-escalation of ASM was 7 months while the longest was 36 months.

Among the 13 cases of seizure recurrence, 11 (84.6%) occurred within the first year of de-escalation of ASM with more than half (8) recurring within the first six months. Only one of the eight patients had seizure recurrence before completing de-escalation of ASM. Two patients had seizure recurrence in the second year following de-escalation of ASM. Anti-seizure medications were re-

started in 11 (84.6%) of the thirteen patient who experienced seizure recurrence.

Focal onset seizure type was associated with a significant risk of seizure recurrence (OR 13.7; 95% CI 0.97, 193.54; p = 0.011). Age at epilepsy diagnosis, duration of epilepsy, biological sex, abnormal EEG at epilepsy diagnosis and before ASM de-escalation, abnormal MRI findings, first or second degree relative, seizure burden and use of two or more ASMs were not associated with increased risk of seizure recurrence on univariable analysis (Table 1).

Discussion

In this study, three quarters of the children with epilepsy whose anti-seizure medications were de-escalated and withdrawn remained seizure for at least 24 months. This is consistent with what has been reported in other studies [1,3]. The median duration of seizure free period before de-escalation in this study was 24 months which may have contributed to the low seizure recurrence rates in this cohort. A seizure-free duration of less than 24 months was found to be the single most significant determinant of seizure relapse in a recent study [6]. The was no statistically significant difference in the median duration of treatment prior to de-escalation of ASM between those who remained in remission and those whose seizures recurred in this study.

Majority of instances of seizure recurrences occurred within twelve months of the initial de-escalation suggesting that patients require close follow-up within the first 12 months after de-escalation. Similar seizure recurrence patterns have been reported in other studies [1,7].

Focal onset seizure type was the only factor found to be significantly associated with increased risk of seizure relapse in this study. Focal onset seizure type was an independent predictor of seizures in the last year of follow-up in a *meta*-analysis [2] but this not been observed in individual studies. This observation could be on account of structural or localized pathophysiological processes which are unlikely to resolve spontaneously and present continued epileptogenic foci. However, the number of patients with focal onset seizures in the present study was low which limits the strength of this association.

Age at epilepsy diagnosis, duration of epilepsy, sex, abnormal EEG at epilepsy diagnosis and before ASM de-escalation, abnormal MRI findings, first or second degree relative with epilepsy, seizure burden and use of 2 or more ASMs were not associated with increases risk of seizure recurrence on univariable analysis in this cohort. In a systematic review and *meta*-analysis of studies across

Table 1
Demographic characteristics and risk factors for seizure recurrence.

Variables	Remission	Relapse	OR (95% Confidence Interval)	P value
Age at Withdrawal of ASM (Mean; Years)	6.37 (95% CI 5.39,7.35)	7.39 (95% CI 4.98, 9.80)		0.336
Age at Withdrawal of ASM (Median; Months)	67.4 (IQR 48.2,112.5)	81.7 (IQR 55.8,134.4)		0.405
Duration of Epilepsy at Withdrawal (Median: Months)	33.0 (IQR 27.8–43.4)	29.4 (IQR 26.9, 33.7)		0.16
Duration of Treatment at Withdrawal of ASM	24.6 (IQR 21.7,31.2)	26.1 (IQR 22.3,34)		0.59
Duration Since Last Seizure (Months)	24 (IQR 23,24)	24 (IQR 16,25)		0.7
	n (%)	n (%)		
Biological Sex				
Male	26 (72.2)	9(69.2)		
Female	10 (27.8)	4 (30.8)	0.87 (0.21, 3.51)	0.84
Seizure Type				
Generalized onset	32 (88.9)	7 (53.8)		
Focal onset	**1 (2.8)**	**3 (23.1)**	**13.7 0.97,193.5**	**0.011**
MRI Findings				
Normal	21 (80.8)	9 (69.2)		
Abnormal	5 (19.2)	4 (30.8)	1.87 (0.39, 8.9)	0.426
No of ASM used				
One	21 (58.3)	9 (69.2)		
Two or more	15 (41.7)	4 (30.8)	0.62 (0.15, 2.45)	0.49
Developmental delay				
No	28 (80)	8 (61.5)		
Yes	7 (20)	5 (38.5)	2.5 (0.59, 10.48)	0.194
First or second degree relative with epilepsy				
No	18 (64.3)	4 (44.4)		
Yes	10 (35,7)	5 (55.6)	2.25 (0.47, 10.81)	0.298
No of seizures before remission				
Less than 10	30 (83.3)	12 (92.3)		
≥10	6 (16.7)	1 (7.7)	0.417 (0.45, 3.383)	0.428
Age at diagnosis of Epilepsy				
<72 months	9 (25)	5 (38.5)		
≥72 months	27 (75)	8 (61.5)	0.533 (0.139, 2.054)	0.357
Initial EEG results				
Normal	15 (42.9)	4 (33.3)		
Abnormal	20 (57.1)	8 (66.7)	1.5 (0.37, 6.05)	0.566
EEG before de-escalation of ASM				
Normal	19 (65.5)	5 (55.6)		
Abnormal	10 (34.5)	4 (44.4)	1.52 (0.32, 7.15)	0.5933

children and adult populations the independent predictors of seizure recurrence were; epilepsy duration before remission, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, developmental delay, absence of self-limiting epilepsy syndrome and epileptiform abnormalities in EEG before withdrawal of ASM. These factors were incorporated in the Lamberink seizure prediction model [2] the accuracy of which has been a subject of validation studies [6,9]. We did not sub-classify the abnormal neuro-imaging findings and the EEG abnormalities included both epileptiform and background abnormalities. The latter may have affected the results.

The main limitations of this study are the small sample size, retrospective design and potential for selection bias given that the study was done at a tertiary referral institution.

Conclusion

Focal onset seizure was the only factor associated with increased risk of seizure recurrence in our cohort. Seizure freedom rate was 76.5% after 24 months following de-escalation of ASM. Majority of the seizure recurrence occurred with the first 12 months of de-escalation of ASM.

Ethical considerations

Permission to review patient records was obtained from The Scientific and Ethics committee of the Aga Khan University Hospital, approval number 2020IERC-145. Data collected were de-identified, coded and stored in a secured data base. For patients who were not on active follow up, a structured document to obtain verbal consent was read out at the commencement of the interview then verbal telephonic consent was obtained from the parent/guardian before obtaining the requisite information related to the study. The interviewer also requested the study participant for permission to record the telephone conversation. An approved phone script prepared in advance was used to guide the brief interview on the two-year outcome for this group of subjects.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Verrotti A, D'Egidio C, Agostinelli S, Parisi P, Spalice A, Chiarelli F, et al. Antiepileptic drug withdrawal in childhood epilepsy: what are the risk factors associated with seizure relapse? Eur J Paediatr Neurol 2012;16(6):599–604.
[2] Lamberink HJ, Otte WM, Geerts AT, Pavlovic M, Ramos-Lizana J, Marson AG, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. Lancet Neurol 2017;16(7):523–31.
[3] Olmez A, Arslan U, Turanli G, Aysun S. Risk of recurrence after drug withdrawal in childhood epilepsy. Seizure 2009;18(4):251–6.
[4] Ou S, Xia L, Li R, Wang L, Xia L, Zhou Q, et al. Long-term outcome of seizure-free patients and risk factors of relapse following antiepileptic drug withdrawal. Epilepsy Behav E&B 2018;88:295–300.
[5] Strozzi I, Nolan SJ, Sperling MR, Wingerchuk DM, Sirven J. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev. 2015(2):CD001902.
[6] Contento M, Bertaccini B, Biggi M, Magliani M, Failli Y, Rosati E, et al. Prediction of seizure recurrence risk following discontinuation of antiepileptic drugs. Epilepsia 2021;62(9):2159–70.
[7] Pavlovic M, Jovic N, Pekmezovic T. Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. Seizure 2011;20(7):520–5.
[8] Zou X, Hong Z, Chen J, Zhou D. Is antiepileptic drug withdrawal status related to quality of life in seizure-free adult patients with epilepsy? Epilepsy Behav E&B 2014;31:129–35.
[9] Lin J, Ding S, Li X, Hua Y, Wang X, He R, et al. External validation and comparison of two prediction models for seizure recurrence after the withdrawal of antiepileptic drugs in adult patients. Epilepsia 2020;61(1):115–24.
[10] Samia P, Barr A, Levi SB, Donald KA, Wilmshurst JM, Newton CR. Clinical characteristics of children with epilepsy managed at an urban hospital in Africa: a retrospective study. J Int Child Neurol Assoc 2019.
[11] Snow RW, Williams RE, Rogers JE, Mung'ala VO, Peshu N. The prevalence of epilepsy among a rural Kenyan population. Its association with premature mortality. Trop Geogr Med 1994;46(3):175–9.
[12] Ngugi AK, Bottomley C, Scott JA, Mung'ala-Odera V, Bauni E, Sander JW, et al. Incidence of convulsive epilepsy in a rural area in Kenya. Epilepsia 2013;54(8):1352–9.
[13] Ba-Diop A, Marin B, Druet-Cabanac M, Ngoungou EB, Newton CR, Preux P-M. Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa. Lancet Neurol 2014;13(10):1029–44.