



## Research Article

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# Risk of Seizure Recurrence after Withdrawal of Antiepileptic Drugs in Multiply Handicapped Egyptian Children with Epilepsy

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## Abstract

**Objectives:** To determine the incidence and risk factors of seizure recurrence in multihandicapped Egyptian children with epilepsy after withdrawal of antiepileptic drugs (AEDs).

**Methods:** This was a prospective study from January 1995 to January 2016. The study population was multihandicapped children with epilepsy followed up in the outpatient clinic of Centre for Children with Special Needs; Egyptian Integrated Care Association (CCSN; EICA), Cairo, Egypt. The eligible children were less than 13 years, seizure-free for at least 24 months, with two normal EEG records, separated by 6 months. The AEDs were withdrawn slowly. The patients were then followed up to look for seizure recurrence.

**Results:** One hundred sixty-two children were recruited in the study. The average age of onset of epilepsy was 14 months. Most patients had partial seizures (49%). Most were controlled on monotherapy (64.2%), and were treated with Phenytoin (24%), Carbamazepine (20.4%), and Sodium valproate (16%). The seizure free duration before starting to withdraw AED was 48.3±9 months. None of the patients had seizure recurrence while the AEDs were being tapered. There were 77 patients (47.5%) with seizure recurrence. The average duration of follow-up for the patients who did not have seizure recurrence was 45±3 months. Most of recurrences occurred in the first twelve months, remainder during next twelve months. The risk factors of seizure recurrence were abnormal neurological examination, the need for use of polytherapy, presence of abnormal findings on brain imaging (CT and/or MRI).

**Conclusion:** Risk of seizure recurrence after AED withdrawal in multiply handicapped Egyptian children was high at 47.5%.

## Introduction

Seizure is a common neurological disorder in children [1,2]. Antiepileptic drugs (AEDs) are usually used for long-term. The medication is only tapered after a seizure-free interval to minimize the risk of recurrence [3,4]. There are many studies on the risk of seizure recurrence after withdrawal of AEDs, which varies from 10% to 50%, partly depending on the study designs [3-7]. The risk factors of seizure recurrence identified include older age of onset of epilepsy, remote symptomatic epilepsy, abnormal electroencephalography (EEG), some epilepsy syndromes such as juvenile myoclonic epilepsy, severity of epilepsies, and those with family history [8-15]. There are to date only rare reports on risk of seizure recurrence after AED withdrawal in Egypt. The objectives

of this study were to determine the incidence and risk factors of seizure recurrence in multihandicapped Egyptian children with epilepsy after withdrawal of antiepileptic drugs (AEDs).

## Methods

This was a prospective study from January 1995 to January 2016. The study population was Egyptian multihandicapped children with epilepsy followed up in the outpatient clinic of Centre for Children with Special Needs; Egyptian Integrated Care Association (CCSN; EICA), Cairo, Egypt. The eligible children were less than 13 years, seizure-free for at least 24 months, with two normal EEG records, separated by 6 months. All patients were subjected

to thorough clinical examination, EEG records, and brain imaging (CT and/or MRI). The AEDs were withdrawn slowly. The exact duration, over which the AEDs were withdrawn, however, varied among the patients, based on the joint decision of the attending physicians, parents, and the patients. If the patients were receiving more than one AEDs, the AEDs were withdrawn sequentially with each AED being withdrawn over at least 3 months. After total drug withdrawal, the patients were then followed up to look for seizure recurrence.

### Statistical Analysis

A survival analysis was performed with seizure recurrence as the hazard ratio and the interval of seizure recurrence (failure time) start after complete drug withdrawal. Log rank test was used for univariate analysis and Cox proportional-hazard model was used for multivariate analysis for risk factors of seizure recurrence. All statistical tests were 2-tailed. The p-value of less than 0.05 was regarded as statistically significant.

### Results

A total of 162 patients (85 Males and 77 Females), selected from population of 7568 patients, were enrolled in this study, which was from January 1995 to January 2016. The characteristics of patients are shown in Table 1.

**Table 1:** Characteristic of the patients with AED withdrawal (n=162).

	Characteristic	No of Patients (%)
1	Male: Female	85: 77
2	Age at onset of epilepsy in months	14 (range 4-39 Ms)
3	Types of seizures	68 (41.9 %)
	a. generalized	
	b. partial	80 (49 %)
	c. undetermined	14 (8.6 %)
4	Antiepileptic drug (AED)	39 (24 %)
	a. Phenytoin	
	b. Carbamazepine	33 (20.4 %)
	c. Sodium valproate	26 (16 %)
	d. others	6 (3.7 %)
5	Patients taking 2 AEDs or more	58 (35.8 %)
6	Seizure-free duration before starting to withdraw AED in months	48.3±9 (range 36-64)

As shown, the average age at onset of epilepsy was 14 months (range 4-39 Ms). The most common seizure was partial (49 %). Most patients were treated with monotherapy (64.2%). Phenytoin, Carbamazepine and Sodium Valproate were the AED used (24 %,20.4 % and 16 % respectively). Seizure-free mean duration before starting to withdraw AED in months was 48.3 months (range 36-64).

Disabilities in the study group were cerebral palsy (CP) in 47 patients (Spastic quadriplegia CP in 8, Spastic hemiparesis CP in 12, Spastic paraparesis CP in 13, Ataxic CP in 6 and Choreoathetotic CP in 8), mental retardation in 129 patients, sensory deficits in 20 patients and behavioral disturbances in 38 patients (Table 2).

**Table 2:** Frequency of types of disability in the 162 patients and its percentage.

Group	No of Patients	Prevalence of Specified Disability
Total study group	162	
Cerebral Palsy (CP)	47	29%
Spastic quadriplegia CP	8	4.9%
Spastic hemiparesis CP	12	7.4%
Spastic paraparesis CP	13	8%
Ataxic CP	6	3.7%
Choreoathetotic CP	8	4.9%
Mental Retardation	129	79.6%
Behavioral Disturbances	38	23.5%
Sensory deficits	20	12.3%

Proposed factors associated with development of epilepsy in the study group include neonatal seizures in 78 patients, positive family history in 47 patients, computerized tomography (CT) brain scanning abnormalities in 99 patients and magnetic resonance brain imaging (MRI) abnormalities in 126 patients (Table 3).

**Table 3:** Proposed factors associated with development of epilepsy in the study group.

	Epileptic (n=162)	Percentage
Female/Male	77/85	
Neonatal seizures	78/162	48 %
Positive family history	47/162	29 %
MRI abnormalities	126/162	77.8 %
CT scan abnormalities	99/162	61.1 %

The average duration of follow-up for the patients who did not have seizure recurrence was 45±3 months. None of the patients developed seizure recurrence while the AEDs were being tapered. There were 77 patients (47.5%) who developed seizure recurrence after AED withdrawal. The incidence density was 0.010 person/months. Most of recurrences occurred in the first twelve months, remainder during next twelve months. The average interval after AED withdrawal when seizure recurrence occurred was 8±11 months (range 2–23 months). Most of those with seizure recurrence had partial seizures. The details of patients with seizure recurrence are shown in Table 4.

Univariate analysis was performed for risk factors of seizure recurrence as shown in Table 5. The risk factors for seizure recurrence are patients who required polytherapy, suffer neurological deficits, and have brain imaging, either CT or MRI, abnormalities. Multivariate analysis was also performed for risk factors of seizure recurrence as shown in Table 6, patients who needed polytherapy for control of their seizures had significant risk of recurrence with hazard ratio of 4.22 when compared to those controlled with monotherapy. Table 6 shows, also, that patients suffering neurological deficits had significant risk of recurrence with hazard ratio of 5.71, and patients with CT or MRI, abnormalities had significant risk of recurrence with hazard ratio of 2.9 Table 5 & 6.

**Table 4:** Characteristic of patients with seizure recurrence (n = 77 cases).

Group	No of patients	Percent of total	Types of seizure	AED	EEG	Seizure-free duration (months)*	Recurrence duration (months)**	Other associate
1	31	19.1%	Gen		NAD			CT and/or MRI abn in 20
	5			PHT	NAD	38	6-12	CT and/or MRI abn in 3
	4			Carb	NAD	42	2-4	
	3			VPA	NAD	44	3-6	
	1			Others	NAD	39	8	
	18			Polytherapy	NAD	50-52	2-14	CT and/or MRI abn in 17
2	40	24.7%	Part		NAD			CT and/or MRI abn in 24
	6			PHT	NAD	47	3	
	0			Carb				
	5			VPA	NAD	60	2-12	CT and/or MRI abn in 2
	3			Others	NAD	58		
	26			Polytherapy	NAD	55-64	4-23	CT and/or MRI abn in 22
3	6	3.7%	Undet		NAD			CT and/or MRI abn in 3
	1			PHT	NAD	37	2	
	1			Carb	NAD	42	6	
	0			VPA				
	0			Others				
	4			Polytherapy	NAD	50-64	4-18	CT and/or MRI abn in 3

\*Seizure-free duration before commencing AED withdrawal

\*\*Interval after AED withdrawal when seizure recurrence occurred

AED = antiepileptic drug, Gen = generalized seizures, Part= partial, Undet= undetermined PHT = phenytoin,

VPA = valproic acid, Carb= Carbamazepine FC = febrile convulsions, EEG = electroencephalography, NAD = no abnormality detected, MRI abn= Magnetic Resonance Imaging Abnormality.

**Table 5:** Univariate analysis by Log rank test for risk factors of seizure recurrence.

Variable	Total No	Recurrence No	% of 77 recurrence	Incidence rate	p-value Significance
1 Male	85	43	55.8	0.011	Non Significant
2 Female	77	34	44.1	0.009	
3 Generalized seizure	68	31	40.2	0.010	Non Significant
4 Partial seizure	80	40	51.9	0.011	
5 Undetermined	14	6	7.7	0.009	
6 AED monotherapy	104	29	37.6	0.006	Significant 0.001
7 2 AEDs polytherapy	58	48	62.3	0.018	
8 Neonatal seizures	78	17	22.1	0.004	Non Significant
9 Positive family history	47	9	11.6	0.004	
10 Neurological deficits	67	59	76.6	0.019	Significant 0.001
11 No Neurological deficits	95	18	23.4	0.004	
12 MRI abnormalities	126	47	61	0.008	Significant 0.01
13 No MRI abnormalities	36	6	7.8	0.003	
14 CT scan abnormalities	99	32	41.6	0.007	Significant 0.01
15 No CT scan abnormalities	63	8	10.4	0.002	

**Table 6:** Multivariate analysis by Cox proportional-hazard model for the risk factor of seizure recurrence.

	Variable	Hazard ratio	95% CI	P-value / Significance
1	Polytherapy	4.22	1.6-19.4	Highly Significant 0.001
2	Neurological deficits	5.71	1.3-23.5	Highly Significant 0.001
3	CT or MRI, abnormalities.	2.90	2.6-15.2	Significant 0.01
4	Age at onset of epilepsy	0.99	0.99-1.06	Non-Significant
5	Partial seizures	1.04	0.07-13.67	Non-Significant
6	Seizure free interval	1.03	0.98-1.05	Non-Significant
7	Female	0.86	0.18-2.91	Non-Significant

## Discussion

Risk of seizure recurrence after AED withdrawal in the study group of multiply handicapped Egyptian children was 47.5% in accordance with many international published materials. There is a number of characteristics in our cohort, which may explain the higher rate of seizure recurrence. Our patients consist of multiply handicapped, with average age of onset of epilepsy of 14 months, frequent neurological deficits (41%), and abnormal brain imaging. Children, with those characteristics, have been shown to have guarded prognosis after AED withdrawal<sup>15</sup>. The proportion with neurological deficits in our cohort is relatively high at 41%. For example, the proportion with neurological deficit in the MRC trial was 22-24%.<sup>9</sup> Remote symptomatic epilepsy, presence of neurological deficits particularly mental retardation, have been shown to be associated with poorer prognosis [8-16]. The average seizure free duration before commencing AED withdrawal in our patients is 48.3 months, which is relatively long. Longer period of seizure freedom before AED withdrawal is associated with lower seizure recurrence [7,17]. In this study, we found that patients with polypharmacy had the risk of seizure recurrence four times more than monotherapy. Not surprisingly, patients who needed polypharmacy reflect their disease being more severe than those requiring monotherapy. We found that patients with neurological deficits had the risk of seizure recurrence more than five times more than who suffer no neurological deficits. Not surprisingly, patients who suffer neurological deficits reflect their disease being anatomical and more severe than those without anatomical lesions. We could not find types of seizure, age at onset of epilepsy, sex, and seizure-free interval during medication as risk factors of recurrence which are different from previous studies [8-12,18]. EEG abnormalities which have been shown to be a risk factor of recurrence<sup>10</sup> were excluded from our group as we put an inclusion criteria that the eligible children were less than 13 years, seizure-free for at least 24 months, with two normal EEG records, separated by 6 months.

## Conclusion

Risk of seizure recurrence after AED withdrawal in multiply handicapped Egyptian children, in this study, was high at 47.5%.

## Acknowledgement

None.

## Conflict of Interest

No conflict of interest.

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