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Seizure outcome and epilepsy patterns in patients with cerebral palsy

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ABSTRACT

Purpose: The aim of the present study was to investigate epilepsy patterns and outcomes in patients with cerebral palsy (CP) and identify the variables that determine remission.

Methods: This was a retrospective cohort study. We followed 107 CP patients aged 1–16 years with newly diagnosed epilepsy. The patients were categorized according to their remission outcome, uninterrupted freedom of seizure for 2 years or longer, and 4 epilepsy patterns: A) sustained freedom from seizures before 6 months of treatment; B) delayed but sustained seizure freedom; C) relapsing-remitting course; and D) seizure freedom never attained. The variables were analysed for their prognostic relevance to the outcomes

Results: A total of 107 patients were included; their mean age at epilepsy diagnosis was 4.2 years (SD 2.5). By the end of the 8-year follow up, 19.6% 26.1%, 31.7%, and 22.4% were in sustained remission, terminal remission, relapse, and no remission respectively. Pattern A was identified in 6.5% of the patients, pattern B in 27.1%, pattern C in 43.9%, and pattern Din 22.4%. Univariate analysis revealed that the type of CP, mobility, and number of seizure types, are among the other factors that significantly affected remission.

Conclusion: A total of 45% of patients with CP and epilepsy achieved remission (with and without antiepileptics) but after a relatively long treatment duration. Remission was affected by patient- and epilepsy-related factors. More studies are required to further evaluate these factors.

1. Introduction

Cerebral palsy (CP) refers to a group of non-progressive motor disorders secondary to lesions or anomalies of the developing brain [1].It has a reported prevalence of approximately 1.5–3 per 1000 [2]. There is a high association between CP and epilepsies. Epilepsies affect between 15–55% of children and adults with CP, compared with 3–6 per 1000, in the general childhood population [3]. Children with CP are prone to many types of seizures and epilepsy syndromes. In most children, epilepsy is treated with antiepileptic drugs (AEDs), but dietary therapy or surgical intervention can be relevant for some [4].

Epilepsy remission is the ultimate goal of epilepsy treatment. The International League Against Epilepsy (ILAE) has proposed a definition of remission as 10-years seizure-free, of which at least the last 5 years are without AEDs use [5]. However, most studies use either a 2 or 5 year seizure-free definition of remission, with or without AEDs [6]. Usually CP patients had been included in the cohort of these studies, which does not allow a clear idea about the seizure outcomes or epilepsy patterns specific to CP. In more CP oriented studies, Skatvedt observed a remission of epilepsy in 43.5% of 46 children with cerebral palsy after 1 year of follow-up [7]; Aksu observed that only 14% of his patients stopped medication after 2 years seizure free, with a relapse rate of 62%. [8]; and Delgado and colleagues followed their CP patients for 2 years after they stopped AEDs or until relapse, whichever was sooner, and they found that 41.5% of their patients had seizure relapses after 2 years seizure-free [9]. Although these studies provided insights into the prognosis of epilepsy in CP, the duration of follow-up was shorter than required by the proposed definitions [5].

The aim of this study was (1) to assess seizure outcome and epilepsy patterns in CP patients with epilepsy over an 8 year period; and (2) to identify factors that likely affect seizure outcome.

2. Patients and methods

2.1. Location

This study was conducted at the neurology outpatient clinics, of Mansoura University Children Hospital, a referral hospital serving 5 governorates in Egypt. Patients are usually referred from both general hospitals and private clinics for both diagnosis and treatment.

Abbreviations: CP, cerebral palsy; AEDs, antiepileptic medications; GMFCS, gross motor function classification system

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2.2. Patients

CP patients, who first developed epilepsy and started treatment in January 2009 to January 2010, were retrospectively followed for 8 years ending January 2017 to January 2018 to determine their epilepsy patterns and outcomes.

The inclusion criteria were as follows 1) age 1–16 years, 2) fulfillment of CP criteria as defined below, 3) diagnosis of epilepsy ascertained by 2 neurologists, and 4) regular follow-up. We excluded the following: 1) patients who did not fulfil the CP criteria defined as below, 2) CP patients with neonatal seizures only, 3) patients with incomplete follow-up for more than a year, and, 4) CP patients with epilepsy who died for reasons not related to epilepsy.

2.3. Definitions

Cerebral palsy was defined as a group of non-progressive disorders affecting movement and posture, and caused by non-progressive insult to the developing foetal or infant's brain [1]. Post - neonatal CP was included as long as the insult occurred before 2 years of age. No lower age was required to ascertain CP. Excluded were patients with: 1) neuromuscular diseases, 2) progressive disorders such as neurodegenerative diseases, and 3) age older than 2 years when the CNS insult occurred.

Seizures and epileptic syndromes were defined and classified according to the ILAE s proposed diagnostic scheme of 2014 [10]. Intellectual disability (ID), was defined as either an impaired cognitive and adaptive functioning in conceptual, practical, and social domains, or an intelligence quotient (IQ) of less than 70 [11].

Seizure outcome was classified according to pre-selected definitions. Multiple studies have used similar definitions in paediatric populations, with variation in the time scale for each definition [12–15]. Remission was defined as a period of uninterrupted freedom from seizures lasting 2 years or longer at any time after diagnosis. It is our policy to stop AEDs if CP patients have been seizure–free for 3 years ; therefore, we examined 3-year, 5-year and 8-year remission periods. Sustained remission was defined as seizure remission for at least 2 years at any time after diagnosis and continuing until the last follow-up. Terminal remission was defined as seizure remission for at least 2 years at the last follow-up with or without previous seizure relapses. A relapse was defined as any seizure recurrence after 2-years of freedom from seizure.

We used epilepsy patterns suggested by Brodie et al. [16] to examine the time to response to AEDs during the course of treatment. In pattern A, patients became seizure-free within 6 months of commencing treatment and remained so throughout follow-up. In pattern B, seizure freedom was delayed for more than 6 months after treatment began, but the patients remained seizure-free throughout follow-up. We did not use an upper limit for pattern B responses; in comparison the original paper by Brodie and colleagues used an upper limit of 12 months. Previous studies in CP and epilepsy suggested that children with these disorders had a delayed response to AEDs compared to normal children, and may require a prolonged period of AED use (3 years rather than 2 years) [17–19]. Patients with pattern C had a fluctuating course, with periods of seizure freedom followed by relapses. These patients were either seizure-free or not at the time of the analysis. Patients exhibiting pattern D never became seizure-free for any 2 year period.

2.4. Methods

For each eligible case, the following data were collected: demographics (date of birth, sex); predominant seizure types; date of diagnosis; epilepsy syndrome if possible; number of AEDs; number of seizure types; EEG findings in the last EEG before withdrawal; IQ if available ; and Gross Motor Function Classification System (GMFCS). The study was approved by the ethical committee of the Pediatrics department, Faculty of Medicine, Mansoura University, written parental consent was obtained for all participants.

2.5. Statistical analyses

SPSS software, version 22.0 (SPSS, Chicago, IL), was used for statistical analysis of the data. Categorical measurements were analysed as the number and percentage, and continuous measurements were analysed as the mean and standard deviation (median and minimum-maximum where necessary). The chi-square test was used for the comparison of categorical measurements to study the predictors of remission (with or without AEDs) versus no remission (relapse and no remission). In the univariate analysis preceding the multivariate, potential prognostic factors were assessed using P-value < 0.05 as a cut-off criterion. The factors that were significantly different between the two groups in the bivariate analysis using the Chi square test ($P < 0.05$) were further analysed with binary logistic regression using a forward Wald method model to determine the predictors. Fitness of model was tested using Hosmer and Lemeshow test. The odds ratio (ORs) and their 95% confidence intervals (CIs) were calculated. A P-value of 0.05 was selected as the cut off for statistical significance. We calculated the relapse rate /year as follows:

Person-years relapse rate (%) = 100_Σ (persons who relapsed/year)/Σ(total persons in total/year)%.

3. Results

3.1. Cerebral palsy patients with epilepsy

During the study year (January 2009- January 2010), 120 CP patients were newly diagnosed with epilepsy. Four patients who died for reasons not related to epilepsy and before completing the follow-up duration, and nine patients who lost follow up for more than 1 year were excluded. A total of 107/120 were included; 61were male and 47 were female. Forty-two patients (39.5%) were born preterm, 56 (52%) and 21 (19.6%) had a family history of epilepsy. Fifty-one patients (47.6%) were mobile (GMFCS level 1, 2, 3) and 56 (52.3%) were non mobile (levels 4 and 5). Forty-six (42.9%) patients had ID. The remaining patients characteristics are presented in (Table 1).

3.2. Epilepsy in CP patients

The mean age at epilepsy diagnosis was 4.2 years (SD 2.5, range 11 month–12 years). Forty five patients had one type of seizure (28 were focal, 17 were generalized), and 62 patients had several types of seizures over time. Sixteen patients fulfilled the criteria for West syndrome, 7 patients had Lennox Gastaut syndrome, and 5 patients had myoclonic astatic epilepsy syndrome.

3.3. Final outcome

By the end of the 8-years follow-up, 19.6% of the patients were in sustained remission (with no AEDs), 26.1% were in terminal remission (with AEDs), 31.7% were in relapse, and 22.4% were in the no remission category. The distribution of types of CP according to seizure outcome is illustrated in (Table 2).

3.4. Outcomes at 3, 5 and 8 years

At 3 years of follow-up, 41 patients (38.3%) had been seizure-free for 2 years and had begun withdrawal of AEDs. Sixty six patients (61.6%) did not have a 2-year period free of seizures. By 5 years of follow-up; 25 patients (23.3%) were in remission with no AEDs, 29 patients (27.1%) were in relapse, 14 patients (13%) were in remission with AEDs, and 39 patients (36.4%) were in no remission. At the 8-years follow-up: 21 patients (19.6%) were in remission with no AEDs, 28 patients (26.1%) were in remission while taking AEDs, 38 patients

Table 1
Clinical characteristics of CP patients with epilepsy.

Variable	Number and percentage
Gender	
Male	61 (57%)
Female	47 (43%)
Consanguinity	56 (52%)
Preterm birth	42 (39.5%)
Family history of epilepsy	21 (19.6%)
Clinical type of CP	
Spastic quadriplegic	33(30.8%)
Spastic hemiplegic	21(19.6%)
Spastic diplegic	23(21.4%)
Dyskinetic	17(15.8%)
Mixed	13(12.1%)
GMFCS	
GMFCS 1	11 (10.2%)
GMFCS 2	15 (14%)
GMFCS 3	25(23.3%)
GMFCS 4	29 (27.1%)
GMFCS 5	27 (25.2%)
Number of seizure types	
One	40 (37.3%)
More than one	67(62.6%)
Epileptic syndrome	
West syndrome	16 (14.9 %)
Lennox Gastaut	7 (6.5%)
Myoclonic astatic epilepsy syndrome	5 (4.6%)
Intellectual disability	46 (42.9%)

GMFCS: Gross Motor Function Classification System.

(35.5%) were in relapse, and 24 patients (22.4%) were in the no remission group (Fig. 1).

3.5. Epilepsy patterns

Pattern A, was observed in 7 patients who became seizure-free in the first six months after beginning treatment, with a mean duration of 3.3 months and an SD of 2.5 months. Pattern B was identified in 29 patients who required more than 6 months to become seizure-free and sustained their remission throughout the follow-up period ; only 2 patients required less than 12 months of treatment, while the rest required a mean duration of 30 months, SD 16.6 months.

We observed the relapsing-remitting course (C) in 47 patients; 13 had early relapses (within the first year of AED withdrawal) but terminal remission, 31 patients did not remit after relapse as of the end of the follow-up period, and 3 patients had late relapse after 5 years free from both seizure and AED use. The reasons for relapse were as follow: 1) withdrawal or cessation of AEDs: 31 patients, 2) changing brands of the same AEDs: 11 patients, 3) unexplained: 4 patients (while on AEDs). The mean duration to relapse for those who had started withdrawal or had already stopped taking AEDs was 15.98, SD 18.8 months (Fig. 1).

Twenty-four patients never had 2 year-seizure free period, consistent with pattern D. They had the following seizure frequencies; daily seizures (3 patients), weekly seizures (2 patients), monthly seizures (9 patients), every few months but less than 6 months (5 patients), and 6–12 months (6 patients).

3.6. AED treatment

By the end of the study, six patients (4 from the relapsing group and 2 from no remission group), chose to stop taking their medications. All six would have one seizure every 9–12 months. Nine patients used one AED, 21 patients (17.7%) used 2 AEDS, 44 patients (41.1%) used 3 AEDs, and 29 patients (27.1%) used more than 3 AEDs. In the relapsing group, 4 patients responded to the same AED they received initially, but the rest of the patients had other AEDs added to their therapy.

3.7. Factors affecting remission

We compared the 49 patients whose seizures stopped (the sustained and terminal remission groups) to the 58 patients whose seizures did not stop (relapsing and no remission groups). In the univariate analysis, many factors affected the remission (P value < 0.05), as illustrated in (Table 3). However, when the significant predictors were analysed by logistic regression, to evaluate the combined effect and determine the most predictive factors, only consanguinity and type of CP were significant. The OR of the number of relapses was 1, indicating that this factor it did not increase the risk in either group (Table 4). It is important to note that highly associated factors were not excluded in the multivariate analysis, because of their importance, which may limit the model.

3.8. Death in CP patients with epilepsy

The causes of death in the patients who passed away during the eight-year period were as follows: 1) respiratory failure following chest infection and ICU admission (year 3) and 2) Sepsis and ileus following gastrostomy procedure (year 5); both of these patients passed away at the hospital. 3) Car accident (after year 3). 4) Death at home following gastroenteritis (year 5). We could not review the death certificates of the last 2 patients. To the best of our knowledge, no patient died unexpectedly in a manner that fulfilled the criteria for sudden unexpected death in epilepsy (SUDP).

4. Discussion

In this study we determined the seizure outcomes and epilepsy patterns of 107 CP patients over an 8-years follow-up period. Regarding outcome, 45.7% of patients had been seizure-free and 54.3% were still having seizures. Nine patients (8%) and 12 patients (11.2%) had been both seizure-free and medication free for 5 years and 2 years, respectively. Sum of 28 patients (26.1%) had been seizure-free for at least 2 years but still on medications. Twenty-four patients (22.4%) had never had a two-year remission period, while 34 patients (31.7%) had relapsed following different periods of remission.

The remission outcome in our study is similar to other studies looked into 2-years outcomes: 12% in Aksu's study [8], 12.9% in Delgado et al. [9], 16% in Kwong et al. [20]. However, the 5-year outcome (8%) was less than (86.6%) in the study by Zafeiriou et al., in which 134 patients discontinued antiepileptic drugs without relapsing in a

Table 2
Types of CP in relation to seizure outcomes.

	Spastic quadriplegic	Spastic hemiplegic	Spastic diplegic	Dyskinetic	Mixed	Total
Remission	2 (9.5%)	2(9.5%)	11(52.3%)	4(19%)	2(9.5%)	21
Terminal remission	4 (14.2%)	3(10.7%)	8 (28.5%)	9(32.1%)	4(14.2%)	28
Relapses	13 (38.2%)	9 (26.4%)	4 (11.7%)	3(8.8%)	5(14.7%)	34
No remission	14 (58.3%)	7 (29.1%)	0	1(4.1%)	2(8.3%)	24
Total	33	21	23	17	13	107

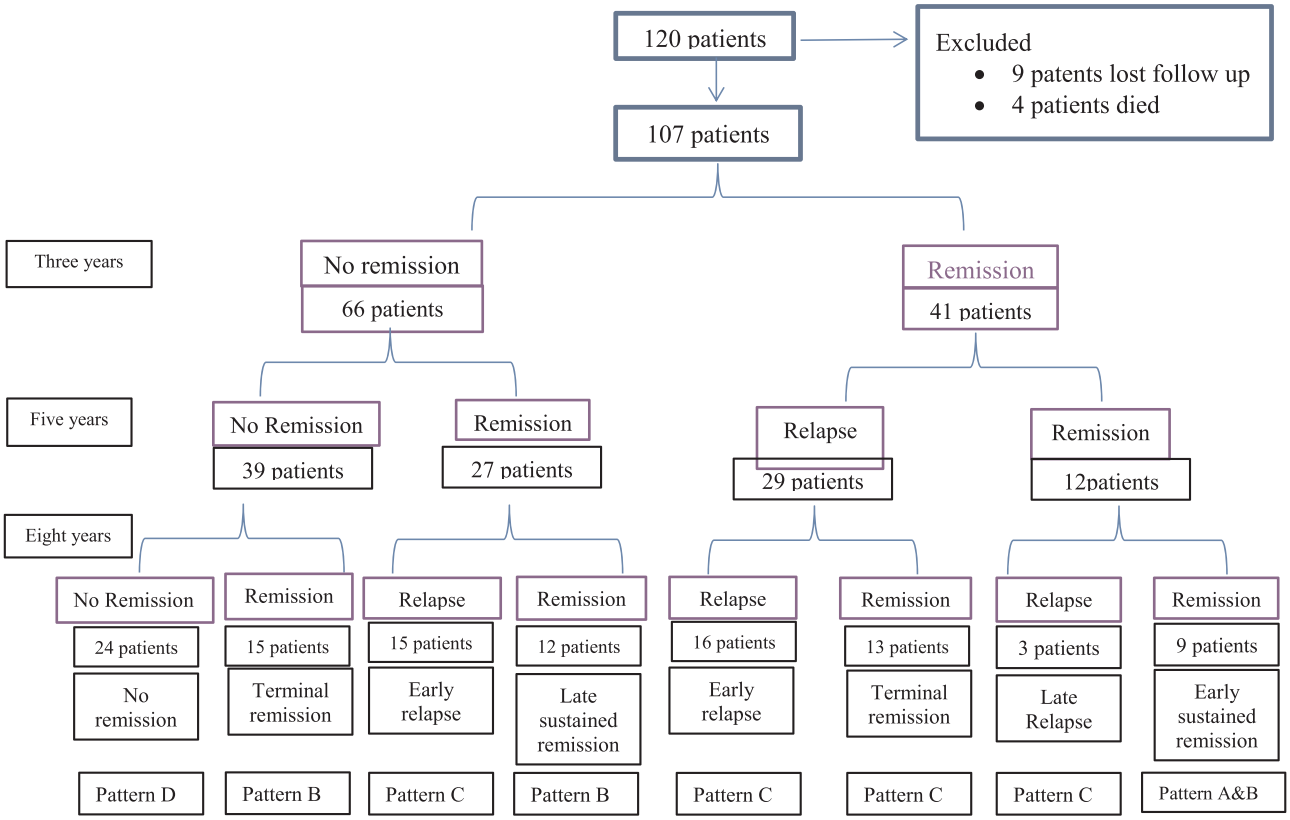

Fig. 1. Patient flow throughout the study in terms of seizure outcome.
Sustained remission: seizure remission for at least 2 years at any time after diagnosis and continuing until the last follow-up. Terminal remission: seizure remission for at least 2 years at last follow-up with or without previous seizure relapses. A relapse was defined as any seizure recurrence after 2-years of freedom from seizures. Early relapse: relapse within first year of seizure-remission. Pattern A, seizure-freedom within 6 months of starting treatment and continuing so throughout follow-up. Pattern B, seizure freedom after 6 months from the start of treatment, and continuing throughout follow-up. Pattern C periods of seizure freedom lasting more than 2-years and interspersed with relapses. Pattern D no seizure freedom for any continuous 2-year period.

follow-up period of 5.8 ± 1.2 years [18].

In comparison to remission of idiopathic epilepsies in children, patients with CP have almost half the chance of remission at 8 years. In the paper by Dragoumi et al., they followed patients with childhood idiopathic epilepsy for a mean period of 8.3 years, 96.3% of their patients were in terminal remission (82, 8% off AEDs and 135% on AEDs) by the end of the study [14].

The most common epilepsy pattern in CP patients was the relapsing-remitting course observed in 43.9% of our patients, which is 2.5 times the percentage reported of the patients (16%) in Brodie et al., 2012 [16]. A study by Geerts et al., that followed patients for a mean of 14.8 years found that 48.4% had a favourable outcome (free of seizures) at the 2nd, 5th and final years of follow-up. Only 8.4% of the patients in our study responded in the first year and continued to be seizure–free until the end of follow-up. This finding indicates that CP patients usually take longer to achieve long-term remission, which may be due to the nature of the cause of CP or the associated comorbidities [21].

We found relapse rates for seizures, to be 27.1 per 100 persons-years in 2015 and 16.8% in 2018, regardless of the cause of the seizures. This finding is consistent with those of previous studies. The reported relapse rate in patients who discontinue AED treatment ranges from 15 ± 70% [14,18,22]. In our participants, seizure recurrence mostly occurred within the first year after AED withdrawal, similar to previous reports.

Ninety patients (85.9%) in our cohort received polytherapy. This is similar to the 82% reported by Aksu [8], but higher than the 45% reported by Kulak et al. [4]. In a prospective multicentre study by Hans et al., that was not limited to CP patients, 80% of the participants were treated with monotherapy and only 20% received polytherapy [23]. The higher use of polytherapy in the current study does not necessarily indicate resistance; rather it reflects a lack of a unified regimen for introducing AEDs among our institution and general hospitals and private clinics. Three patients in our cohort tried a ketogenic diet at a Centre in Cairo, however, none of these patients maintained the diet due to a lack of response after 3–7 months. None of our patients underwent surgical treatment.

Twenty-seven patients failed to benefit from 2 AEDS and required more than 1 year to achieve remission; 12 patients had late sustained remission, and 15 patients had terminal remission. These findings confirm the concept that patients who have failed to achieve remission with two AEDs may still achieve prolonged seizure remission later during follow-up, as previously reported [4,13,24].

We examined several factors and their impact on remission. Male sex, consanguinity, type of CP, prematurity, onset of seizures before 5 years of age, myoclonic seizures, multiple types of seizures, use of more than 2 AEDs, and ID were more prevalent in the no remission group. Neonatal seizures have been reported as an important risk factor for the development of epilepsy in CP patients [20,18,4] ; however in this study they did not affect long-term remission. However in the logistic regression model, only the type of CP and consanguinity persisted as strong predictors of continuing seizures.

Our study has its limitations. First, it was a retrospective study which has implications for data collection. Second, it was not a population-based study which introduces the possibility of referral bias. Third, we did not have a method for measuring patient compliance which might have explained the unexplained relapses.

In conclusion, epileptic patients with CP have a less favourable outcome and a more prevailing relapsing-remitting course; however

Table 3
Univariate analysis of factors affecting remission in patients with CP.

The factor	Remission (no seizures) n (49)	No remission (seizures) (n 58)	P value	Adjusted OR (95%CI)
	Number (%)	Number (%)		
Gender				
Male	21(42.9%)	39(67.2%)	0.01*	2.7 (1.16-6.5)
Female	28(57.1%)	19(32.8%)		
Consanguineous parents	19(38.8%)	40(69%)	0.002*	3.5 (1.4-8.5)
Family history of epilepsy	9 (18.4%)	12(20.7%)	0.7	1.16 .443- 3.036
History of prematurity	13 (26.5%)	28(48.3%)	0.02*	2.5 (1.06-6.4)
History of neonatal seizures	15 (30.6%)	23 (39.7%)	0.3	0.6 (0.3-1.5)
Type of CP				
Spastic quadriplegic	6(12.2%)	27(46.6%)	< 0.001*	21.3(4.5-114.9)
Spastic hemiplegic	5(10.2%)	16(27.6%)	< 0.001*	15.2(2.9-91.7)
Dyskinetic	6(12.2%)	7(12.1%)	0.02*	5.5(0.96-35.1)
Mixed	13(26.5%)	4(6.9%)	0.7	1.5(0.24-8.8)
Spastic diplegic	19(38.8%)	4(6.9%)	1	
Age at diagnosis				
≥ 5yeras	24(49%)	44(75.9%)	.004*	3.3 (1.33-8.12)
< 5 years	25(51%)	14(24.1%)		
History of infantile spasms	6(12.2%)	11(19.0%)	0.3	1.6 (0.5-5.6)
History of myoclonic seizures	12(24.5%)	25(43.1%)	0.04*	2.34 (0.94-5.8)
Number of seizure types				
One	28(57.1%)	17(29.3%)	0.003*	3.2 (1.4-7.7)
Number of AEDs				
≤ 2	21(42.9%)	13(22.4%)	0.02*	2.6 (1.04-6.5)
Mobile patients	29 (59.2%)	22 (37.9%)	0.02*	2.4 (1.02 -5.5)
Patients with ID	9 (18.4%)	37 (63.8%)	< .001*	7.8 (2.9- 21.4)
Abnormal EEG	39(79.6%)	41(70.7%)	0.2	0.6 (0.2-1.5)
Time to first remission				
< 12 months (r)	22(44.9%)	19(32.8%)	1	
12-36 months	13 (26.5%)	15(25.9%)	0.5	1.34(0.46-3.9)
36-60 months	12(24.5%)	0 (22.4%)	0.002*	0.0 (0.00-0.58)
60-72 months	2(4.1%)	0(0)	0.4	0.0(0-5.3)
> 72 months	0(0)	24(41.4%)	< 0.001*	Undefined
Number of relapses				
None	24(41.4)	1	36 (71.4)	24(41.4)
One	14(28.6%)	17(29.3%)	0.2	1.7 (0.67-4.6)
Two or more	0(0)	16(29.3%)	< 0.001*	undefined

Remission: sustained and terminal remission. No remission: relapse and no remission groups.
OR: Odds ratio. CI: Confidence interval. P value < 0.05 is significant.

Table 4
Multivariate analysis of factors affecting remission in patients with CP.

Factor	β	Adjusted OR (95% CI)	P value
Consanguinity	4.4	83.07(8.3-824.12)	< 0.001*
Number of relapses	1		
None	1.03	2.8(0.65-12.06)	0.16
One	24.2	32.2(undefined)	0.9
Two or more relapses			
Type of CP	3.7	42.6(5.6-322.9)	< .001
Spastic quadriplegic	6.3	55.5(33.8-90.9)	< .001
Spastic hemiplegic	2.5	13.05(1.8-91.04)	0.01
Dyskinetic	1.6	5.1(0.6-42.3)	0.1
Mixed	1		
Spastic diplegic			
Constant	−6.06		
Percent correctly	87.9		
predicted	80.4		
Model 2	< .001		
P			

β: Beta coefficients. OR: Odds Ratio. CI: Confidence interval. P value < 0.05 is significant.

long-term remission is possible. Whether longer durations of AEDs, (more than 3 years), might promote sustained remission, requires further prospective studies.

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Declaration of interest

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Author disclosure

Dr. El Tantawi conceptualized and designed the studyconducted the statistical analyses, helped draft the initial manuscript, critically reviewed the manuscript, and reviewed and revised the manuscript. Dr. Abd Elmegid and Dr. Atef helped conduct the study, draft the initial manuscript, helped interpret the results, critically reviewed the manuscript, and reviewed and revised the manuscript. All the authors approved the final manuscript as submitted.

Conflict of interest

All authors have indicated they have no potential conflicts of

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