ORIGINAL ARTICLE

Using Poisson marginal models for investigating the effect of factors on interictal epileptiform discharge in patients with epilepsy

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Background: Epilepsy is a common, chronic neurological disorder that affects more than 40 million people worldwide. Epilepsy is characterized by interictal and ictal functional disturbances. The presence of interictal epileptiform discharges (IEDs) can help to confirm a clinical diagnosis of epilepsy, and their location and characteristics can help to identify the epileptogenic zone or suggest a particular epilepsy syndrome. The aim of this study is to determine the factors that affect IEDs. **Materials and Methods:** Poisson marginal model was done on 60 epileptic patients who were referred to Shefa Neurological Research Center, Tehran, for Video-Electroencephalogram (V-EEG) monitoring from 2007 to 2011. The frequency of IEDs was assessed by visual analysis of interictal EEG samples for 2 h. **Results:** The results show that among age, epilepsy duration, gender, seizure frequency and two common anti-epileptic drugs (Valproic acid and Carbamazepine), only age and epilepsy duration had statistical significant effect on IED frequency. **Conclusion:** Investigating the factors affecting IED is not only of theoretical importance, but may also have clinical relevance as understanding the evolution of interictal epileptogenesis may lead to the development of therapeutic interventions. Generalized estimating equation is a valid statistical technique for studying factors that affect on IED. This research demonstrates epilepsy duration has positive and age has negative effect on IED which means that IED increases with epilepsy duration and decreases with increasing age. So for monitoring IED, we should consider both age and epilepsy duration of each patient.

Keywords: Epilepsy, interictal epileptiform discharge, electroencephalogram, Poisson marginal model, generalized estimating equations

INTRODUCTION

Epilepsy is a common, chronic neurological disorder characterized by recurrent, unprovoked seizures that affects more than 40 million people worldwide.[1,2] Seizures are transient epochs due to abnormal, excessive, or synchronous neuronal activity in the brain.[3] Epilepsy is a generic term used to define a family of seizure disorders. A person with recurring seizures is said to have epilepsy.[4]

Epilepsy is characterized by interictal and ictal functional disturbances. Not only the seizures, but also the interictal epileptiform discharges (IEDs) are associated with neuropsychiatric consequences.[5] Since Gibbs and colleagues discovered spike and wave discharges in epilepsy in 1935, electroencephalogram(EEG) has been used to detect IEDs in patients with a history of seizures.[6,7] Interictal EEG is relatively inexpensive and easy to obtain, recording from scalp electrodes in an outpatient laboratory for 20-40 min. If needed, EEG may be recorded for a longer time either in the laboratory or with a portable recording device for many hours or several days.[6] The presence of IEDs can help to confirm a clinical diagnosis of epilepsy, and their location and characteristics can help to identify the epileptogenic zone or suggest a particular epilepsy syndrome.[8]During IED, specific neuropsychological deficits called transient cognitive impairment (TCI) can be demonstrated. Some patients are clearly handicapped by TCI, and their functioning improves when the IEDs are suppressed by medication.[9] In patients with Landau–Kleffner syndrome, the frequent IED disturb speech functions, resulting in long-term aphasia.[10] Frequent IED may be partly responsible for atypical speech lateralization seen in every fourth patients with left-sided temporal lobe epilepsy (TLE).[11] IED may have an influence on the memory lateralization.[12]

Thus, investigating the factors affecting IED is not only of theoretical importance, but may also have clinical

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relevance as understanding the evolution of interictal epileptogenesis may lead to the development of therapeutic interventions.

Prior studies have demonstrated an increased incidence of IEDs in patients who have had a seizure within the previous two or seven days, but not beyond that period.[13,14] While multiple studies have reported an association between a higher clinical seizure frequency and a greater likelihood of detecting IEDs, or a higher IED frequency, the degree of association is unclear.[5,14-17]This may stem from significant differences in techniques among the published studies, including the EEG recording method by which IEDs were detected and quantified (single routine EEG, multiple serial EEGs, or long-term inpatient EEG monitoring) and the characteristics of the subject cohorts (all epilepsy patients, only those with chronic or medically refractory epilepsy, or elderly patients with epilepsy).[18] Some studies have also reported that increased duration of epilepsy may be associated with an increased likelihood of detecting IEDs or an increased IED frequency.[5,15,16]

Because of the clinical importance of these issues and the lack of Iranian data addressing some of these central questions, the objective of this study is to determine which factors are affecting IED frequency among gender, age, epilepsy duration, seizure frequency and anti-epileptic drugs. We used generalized estimating equations (GEE) for studying the effects of these factors on IED as a Poisson response.

MATERIALS AND METHODS

Patients

In this study, we included 60 patients with epilepsy who presented to Shefa Neuroscience Research Center, Tehran, for V-EEG monitoring from 2007 to 2011. Patients were referred to the center for presurgical evaluations or diagnosis of epileptic or non-epileptic seizures. All patients underwent continuous V-EEG monitoring lasting>2 days. The electrodes were placed according to the modified 10-20 system. Overall 32 electrodes including common and extra electrodes, T9-10, P9-10, FT9-10, FT7-8, were attached to the patient's head. The reference electrodes were the FCz and ground electrode placed on the right shoulder of the patient. The frequency of IEDs was assessed by visual analysis of interictal EEG samples for 2 h.

Our study covered the period from 10-12 am of the second day of hospitalization to record interictal EEG, because at this time all patients had same condition and they were not sleepy, hungry and their drugs were reduced or discontinued at 6 am this day. In order to capture seizures, all patients underwent an antiepileptic drug reduction or discontinuation at 6 am the day after admission. The EEG was analyzed in both bipolar and referential montages. The EEG evaluation was made by electroencephalographers blinded to the objectives of this study and was supervised by one of the authors. In this study, we did not look at the impact of sleep and different sleep stages, the effect of antiepileptic drug reduction, or seizure frequency during the monitoring period.

Statistical method

In medical research, the collection of correlated data is very common. Multivariate observations, clustered data, repeated measurements and longitudinal data are different types of correlated data.[19-21]In longitudinal settings, each individual has a vector Y of responses with a natural (time) ordering among the components. This leads to several models for analyzing this data. In a marginal model, marginal distributions are used to describe the outcome vector Y, given a set X of predictor variables. Alternatively, in a random-effects model, the predictor variables X are supplemented with a vector b of subject-specific effects, conditional upon which the components of Y are often assumed to be independent. Finally, a conditional model describes the distribution of the components of Y, conditional on X but also conditional on (a subset of) the other components of Y. In a longitudinal context, a particular relevant class of conditional models describes a component of Y given the ones recorded earlier in time, the so-called autoregressive or transitional models. The transitional model is used when the analysis must account for a time dependency.[22-25]

The basic premise of marginal model is to make inferences about population means. The term "marginal" is used to emphasize that the mean response modeled is conditional only on covariates and not on unobserved random effects or on previous responses. A distinctive feature of marginal models is that the regression models for the mean response and the model for the within-subject association are specified separately. This separation of the model for the mean response from the model for within-subject association ensures that the marginal model regression coefficient has interpretation that does not depend on the assumptions made about the within-subject association. Specifically, the regression coefficients in marginal models describe the effects of covariates on the population mean response. On the other hand, the basic premise of random-effects model is that there is natural heterogeneity across individuals in the study population in a subset of the regression parameters. That is, a subset of the regression parameters is assumed to vary across individuals according to some underlying distribution. In summary, with random effects model, the main focus is on inferences about each individual, while with marginal models the main focus is on inferences about the study population. As a result, the choice between marginal and random-effects model can only be made on subjectmatter grounds. In our study, we aim to determine the factors that affect on IED in the population of epileptic patient, not for each patient separately, so we use marginal model.[25-28]

In this paper, statistical modeling is based on the IEDs recorded in 4 interval times, 10-10:30, 10:3-11, 11-11:30 and 11:30-12. We selected 10-12 am on the second day of patient's hospitalization to record IEDs, because at this time all patients had same condition and they were not sleepy, hungry and their drugs were reduced or discontinued at 6 am this day. 30-min interval time was selected because the routine time for EEG is about 30 min.

IED as a count is the response variable and the epilepsy duration as the number of years having epilepsy, gender, age, seizure frequency and two anti-epileptic drugs (Valproic acid and Carbamazepine) were considered as covariate variables. The seizure frequency was defined by the number of disabling seizures per month in the 1-year period before hospitalization and was extracted from patients' records.

We use a GEE analysis, assuming a marginal Poisson model with logarithmic natural link function. This model is shown in Eq.1:

$$Y_{ij} \sim Poisson(\lambda_{ij}) \quad i=1,2,\ldots 60,\ j=1,2,3,4 \qquad \text{Eq. (1)}$$

$$\log(\lambda_{ij})=\beta_0+\beta_1(Age_i)+\beta_2(Duration_i)+\beta_3(Seizure\ F_i)+\beta_4(Gender_i)+\beta_5(Valproicacid_i)+\beta_6(Carbamazepine_i) \qquad \text{Eq.1}$$

Because the repeated observations within one subject are not independent of each other, a correction must be made for these within-subject correlations. With GEE, this correction is carried out by assuming *a priori* a certain "working" correlation structure for the repeated measurements of the outcome variable Y. The most commonly used working correlation structures are: 1) exchangeable, in this structure the correlations between subsequent measurements are assumed to be the same, irrespective of the length of the time interval, 2) unstructured, this structure assumes correlations within any two responses are unknown and need to be estimated and 3) autoregressive of first order [AR(1)], assuming the interval length is the same between any two observations. In this study, since the interval times are short and very close to each other it is reasonable to assume that there are no differences between correlations in 4 times. So we suppose exchangeable structure. On the other hand, considering unstructured rather than exchangeable pattern imposes 6 parameters versus 1 parameter in the model, that not necessary.

Statistical modeling and inference was run in SPSS ver.17. Data were reported as frequency (percent) for qualitative variables and mean±standard deviation (SD) for quantitative variables. Exp (β) and their 95% confidence intervals (CIs) were presented and *P* values<0.05 were considered as significant.

RESULTS

In this study, 73.3 and 26.7% were men and women respectively. Their age was in the 7-57 year-old range and their average age was 32.43 ± 12.25 years (mean ± SD). Their average epilepsy duration was 17.12 ± 8.57 years. Their seizure frequency was in the 0-240 range. Among the patients, 73.3 and 55% used Carbamazepine and Valproic acid respectively, 76.7% had partial and 23.3% had general seizure type.

Based on the results, among six covariates only age and epilepsy duration were significant in our model (*P* value<0.05) [Table 1]. *P* value was based on the Wald statistic, which is defined as the square of the ratio between the regression coefficient and its standard error.

Considering the coefficients and the *P* values, patients with longer epilepsy duration had more IEDs than the patients with shorter epilepsy duration. In the other words, 1-year increase in epilepsy duration is associated with a 1.10 increase in IED rate. On the other hand, younger patients had more IED than older one. One-year decrease in age is associated with a 1.06 ($1/EXP(\beta_{age})$) increase in IED rate. Seizure frequency, gender, Valproic acid and

Table 1: GEE results of Poisson model on the six covariates

Variables	Group	No. of subjects	β ± SD	EXP(β)	95 % CI of EXP(β)	*P* value
Age			−0.07 ± 0.03	0.94	(0.88, 0.99)	0.026
Epilepsy duration			0.09 ± 0.04	1.10	(1.01, 1.20)	0.037
Seizure freq			0.002 ± 0.04	1.00	(0.99, 1.00)	0.578
Gender	Male	44	−0.68 ± 0.54	0.51	(0.18, 1.46)	0.209
	Female	16	Reference group			
Valproic acid	Don't use	27	−0.61 ± 0.55	0.55	(0.18, 1.61)	0.273
	Use	33	Reference group			
Carbamazepine	Don't use	16	0.31 ± 0.70	1.36	(0.35, 5.33)	0.656
	Use	44	Reference group			

Carbamazepine did not have statistical significant effect on IEDs.

Estimation of the exchangeable correlation is 0.609, which gives correlation of each pair of IEDs in four time intervals. It suggests that ignoring this strong correlation between IEDs and analyzes the data with common general linear models lead to misleading result.

DISCUSSION

There are many hypotheses about the relation between interictal and ictal epileptic activity. For many years, it has been hypothesized that the temporal summation and spatial spread of IED may evolve to ictal discharges resulting in electroclinical seizures.[29] Recent studies however, indicate that there is no such causal relationship between IED and seizures, and interictal spiking does not increase prior to seizures.[30] IED may represent decreased seizure susceptibility and may inhibit the expression of seizures. [31,32] Jensen and Yaari(1988) demonstrated that seizures are independent of interictal spikes since after the chemical abolition of spike activity or after the disconnection of the spike-generating area from the seizure-generating area, seizures still occur.[33] Some recent studies suggest that IEDs are generated by seizures and this IED-inducing effect of seizures lasts for a long time; Gotman and Maciani(1985) found that IED frequency is highest immediately after the seizures.[34]Janszky *et al.* (2005) found that seizure frequency and epilepsy duration (such as years of patient's life with seizure activity) were independently associated with IED frequency.[6]

In two reports, an association between IED frequency and seizure frequency was noted only when more than one seizure was reported per week in patients undergoing V-EEG monitoring for medically refractory temporal lobe epilepsy.[6,17] among patients older than 65 years at the time of EEG performance, Drury and Beydoun(1998) found an association between increased incidence of IED and a seizure frequency of more than one per month.[16] Similarly, Sundaram *et al.*(1990) evaluated the results of a single routine EEG in adults with clinically definite epilepsy and found an association between increased incidence of IED and a seizure frequency of more than one per month.[14]

There have been variable reports of an association between IED incidence or frequency and epilepsy duration and age at EEG performance. In patients older than 65 years, Drury *et al.*(1998) found no association between IED presence on EEG and age at time of EEG or duration of epilepsy.[16] Similarly, Sundaram *et al.*(1990) found no association between age at time of routine EEG and presence of IEDs.[14] In contrast, in reviewing serial EEGs in patients of all ages, AjmoneMarsan and Zivin(1970) reported a decreasing incidence of IED with increasing age at time of EEG and an increasing incidence of IED with younger age of epilepsy onset.[13] Desai *et al.*(1988) also found an increased incidence of IED in patients with epilepsy duration of greater than 10 years and those with a younger age of epilepsy onset.[15] Janszky *et al.*(2005) noted an increased rate of IED with longer epilepsy duration and no association with age at the time of EEG. The significant differences in subject age ranges, epilepsy characteristics, and types of EEG recording among these published studies provide a likely explanation for the discrepancies in these findings.[6]

In the present study, we examined the effect of age, epilepsy duration, gender, seizure frequency and two common anti-epileptic drugs (Valproic acid and Carbamazepine) on IED frequency with marginal models. Marginal models specify a generalized linear model for the longitudinal responses but also include a model for the within-subject association among the responses. Marginal models do not require distributional assumptions for the observations, only a regression model for the mean response. The avoidance of distributional assumptions for Y_i leads to a method of estimation known as generalized estimating equation (GEE).

Based on the results, among six covariates, only age and epilepsy duration were significant in our model.

CONCLUSIONS

GEE is a valid statistical technique for studying factors that affects on IED. Our findings demonstrated that only age and epilepsy duration had significant effects on IED frequency. Epilepsy duration is positively associated with IED, which means that IED increases with epilepsy duration; on the other hand, age is inversely associated with IED, so IED decreases with increasing age. As a result, for monitoring IED, we should consider both age and epilepsy duration of each patient.

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