

Time Interval Between Traumatic Brain Injury And Post Traumatic Epilepsy

Tempo de Intervalo Entre o Traumatismo Crânio-Encefálico e Epilepsia Pós-Traumática

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ABSTRACT

Introduction. The estimated time interval in which an individual can develop Post Traumatic Epilepsy (PTE) after a traumatic brain injury (TBI) is not clear. **Objective.** To assess the possible influence of the clinical features in the time interval between TBI and PTE development. **Method.** We analyzed retrospectively 400 medical records from a tertiary Brazilian hospital. We selected and reevaluated 50 patients and data was confronted with the time between TBI and PTE development by a Kaplan-Meier survival analysis. A Cox-hazard regression was also conducted to define the characteristics that could be involved in the latent period of the PTE development. **Results.** Patients developed PTE especially in the first year (56%). We found a tendency of a faster development of PTE in patients older than 24 years ($P<0.0001$) and in men ($P=0.03$). Complex partial seizures evolving to generalized seizures were predominant in patients after moderate (37.7%) and severe (48.8%) TBIs, and simple partial seizures evolving to generalized seizures in mild TBIs (45.5%). **Conclusions.** Our data suggest that the first year after a TBI is the most critical period for PTE development and those males older than 24 years could have a faster development of PTE.

Keywords. Craniocerebral Trauma; Epilepsy; Kaplan-Meier estimate; Epilepsy, Post-Traumatic; Brain Injuries.

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RESUMO

Introdução. O intervalo de tempo estimado em que um indivíduo pode desenvolver epilepsia pós-traumática (EPT) após um Traumatismo Crânio-Encefálico (TCE) ainda não é claro. **Objetivo.** Avaliar a possível influência de características clínicas no intervalo de tempo entre o TCE e o desenvolvimento da EPT. **Método.** Foram analisados 400 prontuários de um hospital terciário Brasileiro. Foram selecionados e reavaliados 50 pacientes e seus dados clínicos foram confrontados com o tempo entre o TCE e o desenvolvimento da EPT utilizando uma análise de sobrevivência de Kaplan-Meier. Foi realizada também uma regressão de Cox-Hazard para definição das características que poderiam estar envolvidas no período de latência do desenvolvimento da EPT. **Resultados.** A maioria dos pacientes desenvolveu EPT no primeiro ano (56%). Verificamos uma tendência de desenvolvimento mais rápido de EPT em pacientes maiores de 24 anos ($P<0.0001$) e em homens ($P=0.03$). Crises parciais complexas com generalização secundária foram predominantes em pacientes após TCEs moderados (37,7%) e graves (48,8%) e crises parciais simples com generalização secundária no TCE leve (45,5%). **Conclusões.** Nossos dados sugerem que o primeiro ano após um TCE seja o período mais crítico de desenvolvimento da EPT e que indivíduos do sexo masculino maiores que 24 anos possam desenvolver EPT mais rapidamente.

Unitermos. Traumatismos Craniocerebrais; Epilepsia; Estimativa de Kaplan-Meier; Epilepsia Pós-Traumática; Traumatismos Encefálicos.

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The research was conducted in the Neurology Ward (Department of Medicine) of the Antonio Pedro University Hospital, Niterói, Rio de Janeiro, Brazil.

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INTRODUCTION

Traumatic Brain Injury (TBI) is an event responsible for approximately 5% of all epilepsy cases and 20% of symptomatic epilepsy cases in the United States¹. It is the major cause of epilepsy initiated in young adulthood (15-24 years)². There are few studies about post traumatic epilepsy and TBI characteristics in Brazil and in Latin America. A 1997 research showed that TBI mortality rate in São Paulo, the largest Brazilian city, was estimated at 26 to 39 per 100 000 inhabitants³. In Florianópolis, a retrospective study found that head trauma was the cause of late-onset epilepsy (initiated after 18 years) in 15% of all the 120 patients analyzed⁴ and in another study conducted with 250 patients in Recife, 6.8% of all epilepsy cases were a consequence of TBI⁵.

The “latent period” is considered to be the time between the TBI and the first unprovoked seizure. Preventive treatments and interventions could be focused at this interval⁶, once it is the time after the initial insult that could lead to epileptogenesis, a complex response that includes anatomical changes, neuronal death, initiation of an inflammatory cascade and new genes transcription⁷⁻⁹.

Therefore, the relationship between the type of TBI and the clinical history of the patients should be studied to provide data in order to predict the development of PTE and its “latent period”. This anticipation could lead to several intervention strategies, making the treatment measures more efficient. Also it follows that doctors should have more tools and information about the relationship between variables linked to TBI to predict the development of PTE.

The aim of the present study is to describe the time interval between TBI and PTE development in a population with proved epilepsy and its relationship to TBI severity and clinical features. We also examine possibly influencing factors such as age at the accident, gender, history of immediate or precocious seizures and precocious use of antiepileptic drugs. We describe the incidence of different types of seizures and epileptic syndromes emerging from TBI as well as the rate of pharmacoresistance.

METHOD

We analyzed retrospectively all the 400 patients' medical records from the last 5 years of the Epilepsy

outpatient clinic of the Neurology Service of the Hospital Universitario Antonio Pedro, Universidade Federal Fluminense (HUAP/UFF), Niterói, Brazil. We included and clinically reevaluated 55 patients between 18 and 69 years old at the time of the interview who met criteria of PTE. Patients were advised to attend the medical visit accompanied by at least one relative. From July 2011 to April 2012 patient's relevant data, including laboratory and imaging exams, pharmacotherapy, TBI and seizure characteristics were obtained from both patient interview and previous medical records analysis. Inclusion criteria were: minimum age of 10 years at the time of TBI. We excluded patients that had any type of seizures prior to TBI, diagnosis of primary epilepsy or any predisposing factor for seizures such as family history of epilepsy, central nervous system (CNS) tumors, hippocampal atrophy, metabolic abnormalities or CNS infections. Five patients were excluded from the study according to these criteria.

TBIs were classified according to the most accepted criteria developed by Annegers et al¹⁰. According to these authors, there are three different types of TBI related to injury severity: mild, moderate and severe. Mild injuries were defined as those in which there was no skull fracture and the period of post traumatic amnesia or loss of consciousness lasted 30 minutes or less. Moderate TBIs included patients who had skull fractures or other injuries with more than 30 minutes of post traumatic amnesia or loss of consciousness who did not meet the criteria for a severe injury. The severely injured group of patients included those with a documented brain contusion, an intracerebral hematoma (ICH), or more than 24 hours of post traumatic amnesia or loss of consciousness. Seizures were classified using the classification developed by the International League Against Epilepsy in the 1981 and 1989 criteria^{11,12}.

PTE was characterized as recurrent unprovoked seizures occurring later than one week after TBI. Seizures occurring after TBI were classified as: (1) immediate, when they occurred in the first 24 hours; (2) early, when they occurred after 24 hours and before 7 days; and (3) late, when they occurred after 7 days. Any seizure occurring before 7 days following the accident was classified as a provoked seizure.

Electroencephalography (EEG) results were clas-

sified as normal, abnormal with increased slow activity and abnormal with epileptiform activity for each patient.

We classified patients according to age into children (until 10 years), young people (10 years to 24 years) and adults (older than 24 years) as defined by the World Health Organization in 1986¹³ and grouped them as younger or older than 24 years for analyses procedures.

Statistical analyses were conducted using the software SPSS Version 20 for Windows. The mean was calculated for the quantitative variables and the median for the time interval between the TBI and the PTE due to the asymmetry of values. A Kaplan-Meier survival analysis¹⁴ was used to define the time between the TBI and the first seizure after this event in different groups. To make comparisons between survival curves, a Log-rank (Mantel-Cox) test was used. A Cox-hazard regression was also conducted to define the characteristics involved in the latent period of the PTE development.

The investigators obtained the written informed consent of all patients or of their legal representatives explaining the implication of their participation in the research. The study was approved by the HUAP/UFF ethics committee.

RESULTS

Of 50 patients, 11 (22%) had mild, 14 (28%) had moderate and 25 (50%) had severe TBI. Characteristics of the studied population are summarized in Table 1.

The leading cause of TBI was road traffic accident (RTA) in 30 cases (60%), followed by domestic accidents in 11 patients (22%), falls from height in 4 patients (8%), assault in 3 (6%) and work accidents in 2 cases (4%).

Immediate seizures were seen in 5 cases (10%): 2 in moderate and 3 in severe TBIs. Mild and severe injury groups presented each only one case of early seizure, leading to a total number of 2 cases (4%) of this event in all the studied population.

The most frequent type of seizure was tonic-clonic seizure, seen in 19 patients (38%), followed by complex partial seizure with secondary generalization in 17 cases (34%), simple partial seizure with generalization in 8 patients (16%) and atonic seizure in 1 patient (2%). Of all patients with simple partial seizures with generalization, sensory simple partial symptoms were the commonest, as

observed in 7 patients (87,5%). In mild TBI, the most prevalent type of seizure was the simple partial seizure with generalization (45,5%). In the group with moderate TBI, the most frequent type of seizure was the complex partial with secondary generalization in 5 patients (37,7%). This last kind of seizure was also more frequent in severe TBI, reaching 48% (12 patients). Other types of seizures were not reported.

In the studied population, 86% (43 patients) obtained seizure control with antiepileptic drugs (AEDs). However 39 patients (78%) were on 2 or more AEDs during the research. All data about seizures characteristics and treatments are reported in Table 2.

The median time between the first occurrence of an unprovoked seizure of PTE and the TBI was 12 months. The lower median interval was observed in moderate cases (6 months), followed by both severe (12 months) and mild injuries (12 months). However, these differences between curves were not significant, according to Log-rank (Mantel-Cox) Test ($P=0.89$), used to compare the survival distribution of these samples.

The latent period was associated with two variables: the severity of head injury, considered the most determinant risk factor for development of PTE¹⁵⁻¹⁷ and the age of the patient at the time of the accident, also a risk factor¹⁸. In mild injuries, this interval did not exceed 7 years and the biggest proportion of patients experienced the first seizure in the first year after TBI. In moderate and severe TBIs, more than half of the patients also had the first seizure in the first year, however the beginning of PTE beyond 10 years happened with 2 patients in each case, corresponding to 14,3% of patients with moderate traumas and 8% with severe ones.

Considering the age of patients (younger or older than 24 years old) at the moment of the TBI, a Kaplan-Meier survival analysis was conducted, as showed in Graphic 1. The defined event was the first unprovoked seizure after the TBI. Patients younger than 24 years (34 patients) had a latent period which varied from 8 days to 29 years, and 38.2% of these patients had their first seizure in the first year. Among people older than 24 years (16 patients), the maximum latent period was 3 years and 93.8% of the patients had the first seizure in the first year.

A Kaplan-Meier survival analysis was also con-

Table 1
Characteristics of the study population

	Mild	Moderate	Severe
N (%)	22	28	50
Age, years ^a	35±13	41±12	42±13
Gender (Male/Female) (%)	82/18	57/43	96/4
TBI, age ^a	15±13	23±15	23±15
PTE after TBI, months ^b	12(0,25-84)	6(0,25-348)	12(1-348)

^aMean, ± standart deviaton; ^bmedian (minimum-maximum)

Table 2
Characteristics of the seizures and treatment for each type of TBI

	Total (N=50)	Mild (N=11)	Moderate (N=14)	Severe (N=25)
Immediate/early seizures (%)	10/4	0/9	14.3/0	12/4
Tonic-clonic seizures (%)	38	36.4	28.6	44
Simple partial seizures (no generalization/with generalization) (%)	0/16	0/45.5	0/21.4	0/0
Complex partial seizures (no generalization/with generalization) (%)	6/34	0/0	14.3/37.7	4/48
Atonic seizures (%)	4	9	0	4
Focal seizures (%)	2	9	0	0
Controlled epilepsy (%)	86	81.8	85.7	88
New antiepileptic drug needed (%)	78	90.9	85.7	68

ducted for each severity group according to individual characteristics of the patients. A tendency of a faster development of PTE was found in patients older than 24 years and in men. Significant values were found in gender variable and in patients exposed to mild injuries and in the age variable of patients in moderate and severe TBIs. Difference in mild injuries regarding the age at the time of the TBI could be explained by the low number of patients older than 24 years included in this group (only 1 patient).

To consider the effects of a multivariate analysis, a Cox-hazard regression was also conducted (Table 3) in order to define which features could be involved in the latent period. Variables were chosen according to their significant value in the Kaplan-Meier analysis. Although gender was not a significant variable in moderate and severe TBIs, it was included given its known importance. It is seen that the most determining variable involved in a faster PTE development is moderate TBI exposition, followed by the age of the patient at the moment of the TBI,

severe injuries and the gender, respectively. Men were susceptible to develop PTE faster than women. Only age and gender had statistically significant associations.

DISCUSSION

In this article, we want to access the influence of several factors, in particular accident severity and age at TBI, over the latent period to the beginning of PTE following TBI in a population of 50 patients. Data about treatment and main clinical features were also described in order to give more complete information about the group studied and to make comparisons between variables and outcomes. To our knowledge this is the first study of this type in Brazil.

As in previous studies¹⁹, it is suggested that the development of PTE is higher in the first year after TBI, and also that seizures beginning 10 years after TBI are less usual, but possible^{20,21}. In addition, it has been reported that the standardized incidence ratio of PTE (an estimate of the occurrence of an event) for patients with TBI be-

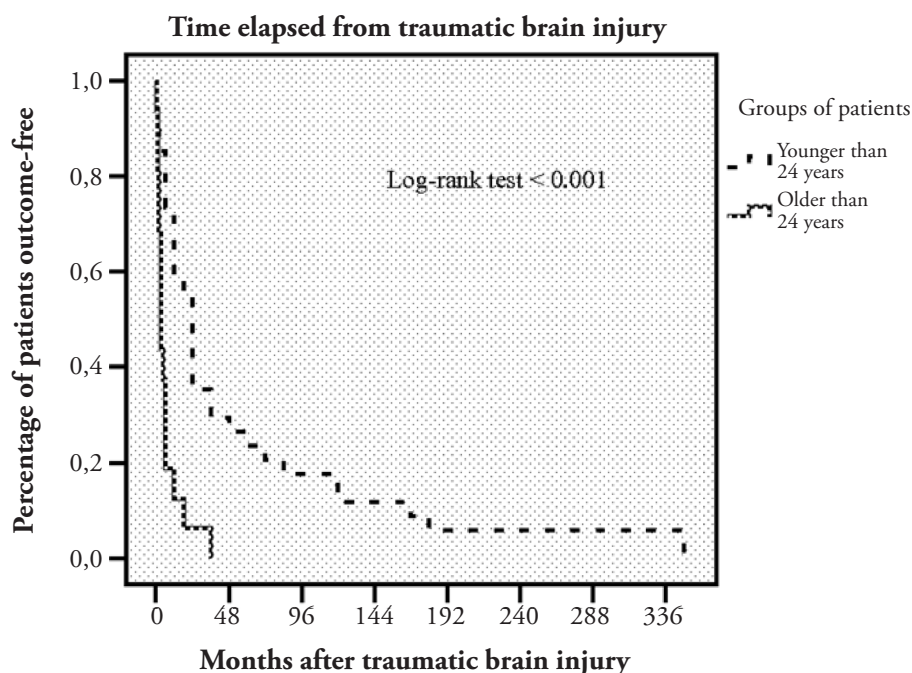


Figure 1. Time elapsed from traumatic brain injury according to age at the time of the traumatic brain injury.

Table 3
Cox Hazard Regression values

Variable	Exp (B) (95%)	P
Gender	0.36 (0.14-0.93)	0.03
Patient age at TBI	1.05 (1.03-1.075)	<0.0001
Mild TBI (Ref. ^a)	1	0.147
Moderate TBI	1.73 (0.82-3.65)	0.152
Severe TBI	0.66 (0.29-1.53)	0.34

^aRef.=Reference category

comes higher according to the gravity of the head trauma, which raises its maximum value in severe TBI and this number persisted for 20 years²⁰. Due to our study, patients older than 24 years had a faster development of PTE when compared with younger patients; we found this tendency of development of PTE even 10 years after the TBI, especially high in patients younger than 24 years. In contrast, we could not find any significant association between the TBI severity and the time interval to PTE development.

The types of seizures associated with different degrees of TBI severities is also an important subject that we attempted to observe in our patients. We found that

each type of TBI was associated with some few possible types of seizure. However, the current literature does not show any clear prediction that can be made^{16,22,23}. A research conducted with 199 veterans from the Vietnam Head injury study (VHIS) showed that complex partial seizures could be seen as a tendency in the later years after a TBI²⁴. We found a high prevalence of generalized seizures in the studied population. Once this kind of seizure has an elevated morbidity due to accident risks, an early prediction of their occurrence is desirable.

The rate of pharmacoresistance in the studied PTE patients was a little lower than that in the general epilepsy population that is nearly 30%^{25,26}. When compared to other types of TBI, our patients with mild injuries had curiously the highest rate of uncontrolled seizures (18.2%), but there are no similar results in literature. We did not find pharmacoresistance to be related to PTE latent period, however some researches show that patients with a PTE development during the first year after TBI are more easily controlled²⁷.

Early antiepileptic drug treatment was reported just by one patient with severe TBI. His PTE latent period, his clinical characteristics, as well as his treatment

course had no significant difference when compared to other patients. This event is consistent with literature that shows no efficacy in protecting against the development of PTE²⁸. These drugs act as anticonvulsant medication, and not as antiepileptogenic agents, which can explain the effectiveness in controlling the early provoked seizures, but not in preventing the initiation of the late seizures²⁹.

Recent researches could not give consistent data about the diagnosis of PTE and EEG; and so was possibly not helpful³⁰. In the 50 patients studied, EEG features had not an important role in predicting PTE latent time.

Limitations of the research were the small number of patients included and the fact that all individuals in the study had a history of both TBI and PTE, so that no inference on PTE incidence in a large population could be made.

CONCLUSIONS

In conclusion, we have observed that most cases of PTE development were initiated in the first year after TBI in all severity groups (mild, moderate and severe TBI). This finding is consistent with literature and should lead clinicians to intensify follow-up, especially in the first year after TBI, no matter its severity.

In the group studied, children and young adult patients seemed to have a slower PTE development time after TBI than adults and elderly individuals. Also the most predominant kinds of seizures were complex partial seizure with generalization in severe and moderate TBI and simple partial seizure with generalization in mild TBI.

Even though the best prophylactic treatment and prevention strategy is not well defined, intervention during the latent time could be an important event for preventing PTE and all its negative impact. Animal models and clinical research trials, besides the new approaches in neuroimaging and in neurophysiology make the PTE epileptogenesis the most possible target and hope of an epileptogenesis inhibiting treatment⁶. Road traffic accident prevention could also be an important strategy to decrease significantly the number of PTE patients once our study showed it as one of the major causes of TBI.

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