

Post-Ischemic Stroke First-Time Seizures: Influence of Gender and Age of the Patient on the Latent Period

Marcelo Moraes Valença¹, Luciana Patrícia A. Andrade-Valença², Gilson Edmar G. Silva¹, José Antunes-Rodrigues³, João Pereira Leite⁴

ABSTRACT

This is a retrospective study performed in order to evaluate the influences that gender or age of the patient may exert over the late initial post-ischemic stroke seizure. The duration of the latent period was significantly longer in men when compared with women [19.07 ± 4.60 months versus 7.67 ± 1.69 months; $P < 0.05$]. In the group of men, six presented the latent period longer than 20 months, whereas in the female group the longest latent period observed was 20 months (men 6/14, 42.9%; women 0/12, 0%; $P < 0.05$). There was no difference in the duration of latent period among different age of the patients. When we analyzed the duration of the latent period versus age of the patients also no statistically differences were detected. In conclusion, the present study demonstrate that the latent period that occurs after acute first-ever ischemic stroke in male patients is longer than that observed in the opposite gender.

Key words: Epilepsy, stroke, latent period, gender, classification, age.

RESUMO

Este é um estudo retrospectivo realizado para avaliar as influências exercidas pelo gênero e pela idade do paciente sobre as crises epiléticas tardias pós-acidente vascular cerebral isquêmico (AVCI; 30 dias após o evento agudo). Foram estudados 26 pacientes (14 homens). Os resultados mostraram que o período latente foi mais longo nos homens quando comparados com as mulheres [19,07 ± 4,60 meses (n = 14) versus 7,67 ± 1,69 meses (n = 12); $P < 0,05$]. Por outro lado, não houve diferença significativa na duração do período latente entre pacientes com idades diferentes. Concluindo, este estudo demonstrou que o período latente que ocorre entre o evento agudo de um AVCI e a crise epilética é maior no homem quando comparado com o gênero oposto.

Palavras chave: Epilepsia, acidente vascular cerebral, período latente, gênero, classificação, idade.

¹ Neurology and Neurosurgery Unit, Department of Neuropsychiatry, CCS, Federal University of Pernambuco, Recife, PE, Brazil.

² Department of Neurology, University of Pernambuco, Recife, Brazil

³ Department of Physiology and ⁴ Department of Neurology, Psychiatry, and Medical Psychology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

Correspondence: Marcelo M. Valença, Departamento de Neuropsiquiatria, CCS, Universidade Federal de Pernambuco, Cidade Universitária, 50670-420 Recife, PE, Brazil.

E-mail: mmvalenca@yahoo.com.br

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INTRODUCTION

Epileptic seizures following ischemic cerebrovascular accident (ICA) are a common sequel of the cerebral hemisphere injury and are particularly prevalent after a cerebral infarction in the carotid artery territory.

In about 15% of the patients, who survive to an acute ischemic stroke, epileptic seizures might occur¹⁻³. Although ICA can occur at any age, it is most frequently in the elderly, a fact that may explain why stroke is the major cause of late-onset epilepsy after age 35 years^{3,4}. Valença and Valença⁵ reported that ICA was the major etiological cause of the epileptic seizures in an adult population studied in Recife, Brazil, affecting 17.3% of the patients. In patients older than 45 years of age the frequency of ICA increased to 36.7%, followed by brain tumors in 12.3%, hemorrhagic cerebrovascular disease in 11.2%, and cysticercosis in 5.1%. In a population-based study So et al.² followed 535 patients from their first cerebral infarction until death or migration out of Rochester, Minnesota. Early seizures (within one week) were present in 33 patients (6%), whereas 27 patients developed initial late seizures more than one week after ICA. The cumulative probability of developing initial late seizures was reported as: 3.0% by 1 year, 4.7% by 2 years, 7.4% by 5 years, and 8.9% by 10 years². An intriguing characteristic of the initial late seizure after brain lesion is the large variability in time duration of the latent period, in which the ischemic brain tissue would turn into a long-lasting potential epileptic region.

In this concern, there are several studies reporting the effects of sex steroid or gender differences observed during experimental epileptogenesis⁶⁻⁸. However, we did not find any report concerning gender influence on post-stroke latent period.

This study was performed in order to evaluate the influences exert by either gender or age of the patient at the moment of the first-ever ischemic stroke over the epileptogenic transformation within the four weeks after an ischemic brain damage.

SUBJECTS AND METHODS

This is a retrospective study involving 26 patients (14 men) with acute first-ever ischemic stroke, who attended the outpatient neurological clinic, Hospital das Clínicas, Federal University of Pernambuco, from 1992 to 1999. Since after an acute brain ischemia reversible anatomic-pathologic changes may persist for 3-4 weeks, we decided to include only cases in which the first epileptic seizure occurred later than four weeks after the cerebral ischemia. Computed tomography and/or magnetic resonance imaging were used to confirm the clinical diagnosis of stroke.

The data are reported as mean \pm SEM. Either one-way Anova, χ^2 test, or Student's t-test was used when appropriate. A *P* value of <0.05 was considered significant.

RESULTS

The Figure 1 shows that the duration of the latent period was significantly longer in men when compared with women [19.07 ± 4.60 ($n = 14$) versus 7.67 ± 1.69 ($n = 12$); $P=0.0389$]. In the group of men, six presented the latent period longer than 20 months, whereas in the female group the longest silent period observed was 20 months (men 6/14, 42.9%; women 0/12, 0%; $P = 0.0171$ Fisher's exact test). No difference was observed in the age of the patient between both genders (man, 61.5 ± 3.1 year-old; woman 58.2 ± 3.3 year-old, $P = 0.4672$). On the other hand, there was no difference in the duration of latent period among different age (one way analysis of variance, $P = 0.3788$). The duration of the latent period had no relationship with the age of the patient at the time of ICA (Tables I and II)

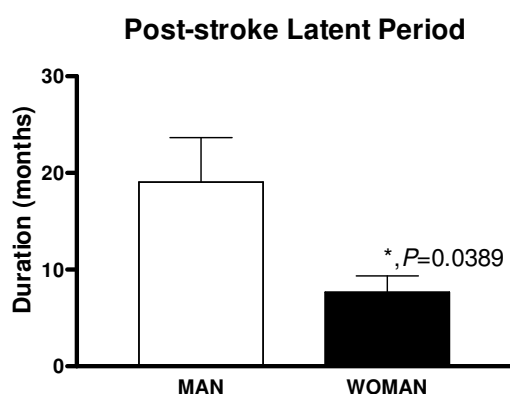


Figure 1: Gender differences in post-stroke latent period. The data are mean \pm SEM (n = 14 and 12, respectively).

Table I: Duration of the latent period observed at different range of the patient age.

Age (years)	Duration (months)	median (months)
38 – 50	9.0 \pm 3.2 (2 – 20; n = 6)	5
51 – 60	18.0 \pm 7.5 (1 – 60; n = 7)	12
61 – 70	9.0 \pm 3.2 (1 – 24; n = 9)	4
71 – 80	19.8 \pm 7.7 (7 – 48; n = 5)	12

The data are mean \pm SEM (lower and higher values).

Table II: Duration of the latent period and age of the patients.

Duration (months)	Age (years)	median (years)
1 – 6	56.3 \pm 3.7 (41 – 70; n = 10)	57.5
7 – 12	64.2 \pm 4.8 (51 – 76; n = 6)	65.5
13 – 18	55.0 \pm 8.7 (38 – 67; n = 3)	60.0
19 – 24	62.2 \pm 3.7 (50 – 72; n = 5)	63.0
> 24	67.5 \pm 8.5 (50 – 76; n = 2)	67.5

The data are mean \pm SEM (lower and higher values).

DISCUSSION

The present study demonstrated that the latent period after acute ischemic stroke was longer in man than that observed in woman, and the age of the adult patient at the time of the ICA did not interfere with the poststroke epileptogenesis.

Gender may influence the latent period in post-stroke seizure by at least two mechanisms: (a) preexistent sexual brain dimorphism that makes the female brain more susceptible and (b) hormonal influence on neuronal reorganization after the ischemic event.

After vascular occlusion brain water reaches its maximum 2-4 days later⁹. In addition, significant changes in blood brain barrier may be observed for 20 days¹⁰. The brain swelling in stroke may be subdivided in three phases: 1. an immediate increase (within first minute) in brain volume due to vasoparalysis (tissue acidosis); 2. a metabolic (cytotoxic) type of brain edema; and 3. a vasogenic brain edema which follows the metabolic type of edema after 4-6 hours, reaching its maximum after a few days. In about 3-4 days after cerebral arterial occlusion it is detected the maximal anatomic deformity, and it is only after this period of time that a gradual reabsorption of the excessive parenchymal fluid takes place¹¹⁻¹⁴.

Seizures after a stroke event were in the past arbitrarily subdivided in early or acute (occurring within the 2-30 days following the stroke) or late (after the 7-30 days following the stroke). Early seizures were defined as those arising after stroke at different intervals, depending on the authors, within 24 hours¹⁵, one week¹⁶, two weeks³, and 30 days after stroke¹⁷. In this concern, we would like to propose a new classification based on the moment that the seizure occurred and the pattern of brain edema that follows the regional ischemia:

- A. At the onset of stroke.
- B. Very early, within the first two days.
- C. Early, from day 3 to day 7 post-stroke.
- D. Intermediate, from second week to fourth week.
- E. Late epileptisy, after 4 weeks.

The limit of four weeks is a tentative to separate seizures due to physicochemical changes (reversible), provoked by the brain injury, from the seizures originated as a result of the anatomopathologic reorganization or evolution to a permanent state of that area of ischemic lesion. Moreover, considering brain trauma, posttraumatic seizures were classified in: (a) immediate (first seizure occurs less than 24 hours of the trauma), (b) delayed early (within a month), and (c) late (later than one month)¹⁸.

Several putative factors may participate in the neuroregeneration and, consequently, in the process of epileptogenesis after a cerebral ischemic insult: age and gender of the patient, genetic factors, use of drugs, physical activity, diet, stress level, life-style, brain area involved, side and topography of the lesion (dominant versus non-dominant cerebral hemisphere), stroke recurrences, type of stroke (ischemic, hemorrhagic, embolic, etc.), size of the ischemic area, associated diseases (i.e., hypertension, diabetes), and other environmental or organic factors.

At the onset of all-type stroke 3.2 % of the patients present seizure, with a relative frequency of 2.9% in ICA, 10.8% in subarachnoid hemorrhage, and 4.6% in intracerebral hematoma¹⁹.

Gender exerts an important influence in brain development and organization, such influences may persist until later in life. Gonadal steroid hormones may exert an important role in the seizure susceptibility⁶⁻⁸. Proconvulsant effects of estrogen have also been reported²⁰, and menstrual cycle effects on cortical excitability suggest a close interrelationship between sex hormone and epilepsy in women²¹. Estrogen may induce synaptic and dendritic remodeling²², increase the density of N-methyl-D-aspartate receptors in hippocampus²³ as well as glial activation²⁴. On the other hand, Briellmann et al.²⁵ reported that in mesial temporal lobe epilepsy women are relatively protected for seizure-associate damage. Side of hippocampal lesion, age of initial precipitant injury (IPI), and latent interval can be influenced by both gender and age of the patient^{26,27}. But this is a different form of epilepsy, in which the IPI occurs often during childhood at an early age.

It is still largely unknown why and how brain cells respond after an injury. A speculative hypothesis would be that surviving neurons, and possibly glia as well, under one new altered environmental condition, occurring after an ischemic lesion, would reorganize in order to recover the lost function. So, epilepsy would be the “price” paid for this functional recovery. It seems that neurons in a tentative to optimize their biochemical or physiologic roles would decrease the threshold of membrane excitability, permitting the cells to fire excessively and in abnormal synchrony. Neuronal changes can be observed minutes to months after focal brain lesion²⁸, as the result of deafferentation, unbalance between excitation and inhibition, changes in membrane excitability, or by facilitating preexisting or new connections^{29,30}.

Other variables might influence the latent period as well. As to the impact of trauma-induced epilepsy, Pailas et al.¹⁸ stated that “the patient’s age at the time of the trauma certainly influences the organization of the epileptogenic focus in children”. When the injury occurred before the age of 3 years, between 7-15 years, and after 15 years, the average delay of the first seizure was 15-16 years, 15 years, and 1-2 years, respectively. In contrast, trauma in patients after 50 years of age usually provokes relative short latent period, within the range of a few months to a few years.

To the best of our knowledge, this is the first study evaluating whether gender of the patient would influence the post-stroke latent period. In conclusion, the present study demonstrate that: 1) the post-stroke latent period in male patients is longer than that observed in the opposite gender. 2) The age of the patient (from 38 to 76 years of age) seems not to interfere with the post-stroke epileptogenesis, at least considering this parameter (*i.e.*, duration of the latent period).

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