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ELECTROENCEPHALOGRAPHIC REACTIVITY AS A PREDICTOR OF PROGNOSIS IN COMATOSE PATIENTS

Nayra Roberta Sales Salvador
Higher academic education: Master's in Neurology
Current Institution: `` Centro de Estudos Superiores de Maceió ``(CESMAC)
Address: Rua Cônego Machado 918, Farol. Maceió – Alagoas.

Maira Medeiros Honorato
http://lattes.cnpq.br/5547870761114176

Erika Lopes Honorato
http://lattes.cnpq.br/3665484453004464

Patricia Serrano Passalacqua
http://lattes.cnpq.br/7741248753521918

Caroline Ferreira Pereira
http://lattes.cnpq.br/9474590325470397

Eliana Garzon
http://lattes.cnpq.br/5216705221454512
Hospital das Clínicas da Universidade de São Paulo

Abstract: Introduction: When vital functions are maintained, but the patient is unconscious, in a coma or in a vegetative state, it is important to predict the chance of regaining consciousness, that is, the ability to carry out simple orders or purposeful reproducible and sustained behavior. Studies suggest that the presence of reactivity on the electroencephalogram (EEG-R) predicts a greater chance of regaining consciousness. The aim of this study is to verify the prognostic value of electroencephalographic reactivity in comatose patients. Methods: The study included EEG of patients who were in a coma without sedation, from June 2016 to June 2017. The presence or absence of electroencephalographic reactivity was verified, and the outcome of each patient was based on the analysis of the medical records after the procedure. minimum of 2 months of follow-up. Data were descriptively analyzed using absolute and percentage frequencies, while Pearson's chi-square test was used to assess the significant association between electroencephalographic reactivity and the chance of regaining consciousness. Results: Of the total of 116 electroencephalographic recordings, traumatic brain injury and hemorrhagic stroke accounted for more than 50% of the causes of coma and death. The percentage that regained consciousness was 46.4% among the EEG-R and was null among the non-reactive ones ($p < 0.01$). Discussion and conclusion: Frequency, amplitude and reactivity of brain electrical activity have been demonstrated as predictors of improvement in coma. The presence of reactivity in the EEG, in this study, was not as favorable as the possibility of improvement in consciousness. However, non-reactive EEG was shown to be strongly related to a poor prognosis. Therefore, it is important to research electroencephalographic reactivity to external stimuli in comatose patients undergoing EEG, as this is a simple, useful and non-invasive method that can provide information regarding the prognosis in coma.
Keywords: coma, reactivity, prognosis

INTRODUCTION

When vital functions are maintained, but the patient is unconscious, in a coma or in a vegetative state, it is important to predict the chance of regaining consciousness, that is, the ability to carry out simple orders or purposeful, sustained and reproducible behavior. Studies suggest that the presence of reactivity on the electroencephalogram (EEG-R) predicts a greater chance of regaining consciousness. (logi, 2011; GangLiu, 2016; Gutling, 1995)

Reactive electroencephalographic pattern was defined as a change in the frequency or amplitude of the baseline activity, detected within a few seconds of stimulus application. (Logi, 2011). There may be an increase in amplitude as well as a decrease, the latter being rarer, however it seems to be associated with a better prognosis (Johnsen, 2018).

In the analysis of brain electrical activity, the dominant frequency, trace continuity, presence of reactivity and occurrence of epileptiform paroxysms can predict prognosis in critically ill patients. Patterns such as generalized suppression (<10mV), burst suppression, epileptiform activities, periodic discharges, monotonous and unreactive alpha-theta rhythms generally have a worse prognosis. (Azabou et al, 2018; Synek 1988).

The stimulus to be offered varies in different studies. Being done frequently, auditory stimuli, such as clapping and calling the name; painful stimuli such as compression of the sternum, compression of the nail bed on each upper limb (Johnsen, 2018; Admiraal, 2019), tactile stimulation, especially the use of a cotton swab in the nasal cavity; visual stimulus with eye opening and closing (Baginati et al), and also somatosensory stimuli, mainly in

the median nerve (Gutling et al, 1995; Young 1999).

Auditory stimuli are mainly used in combination with noxious stimuli or with visual and noxious stimuli. However, the exact frequency and duration of the stimulus are almost never described. (Admiraala, 2016). In the study by Johnsen, 2018, the stimuli were applied for 30 seconds, with a 2-minute interval between them. In general, the first stimulus is the most informative, but the painful stimulus is the most robust. (Tsetsou, 2015).

Several studies associate the absence of electroencephalographic reactivity with a greater chance of death or remaining in a coma (Logi, 2011; GangLiu et al, 2016; L. Li, 2015). The relationship between the presence of reactivity and clinical outcome, however, was variable, with low sensitivity for some authors (Admiraal, 2019).

The aim of this study is to verify the prognostic value of electroencephalographic reactivity in comatose patients.

METHODS

This was a retrospective cohort study conducted by the electroencephalogram sector of ``Instituto Central do Hospital das Clínicas`` at ``Universidade de São Paulo`` in 2017.

The study included electroencephalograms of patients who were in a coma, without the use of sedatives, between the period from June 2016 to June 2017. The presence or absence of electroencephalographic reactivity in these exams was verified, considering EEG-R those that had alterations in the frequency or amplitude in the baseline activity when an external stimulus is applied.

Sound stimuli were used, such as clapping hands and calling the patients' names; painful stimulus with compression of the sternum, and tactile stimulus in both upper limbs.

The outcome of each patient was obtained based on the analysis of the medical records after a minimum of 2 months of follow-up, being divided into those who regained consciousness, remained in a coma or vegetative state, and those who evolved to death. Patients who used sedatives during electroencephalographic reactivity testing or those whose anesthetic medication was withdrawn, but who underwent the test before the end of the half-life of the drug, were excluded from the study. Those with an incomplete clinical evolution record or who were transferred to another hospital before the two-month follow-up period were also excluded.

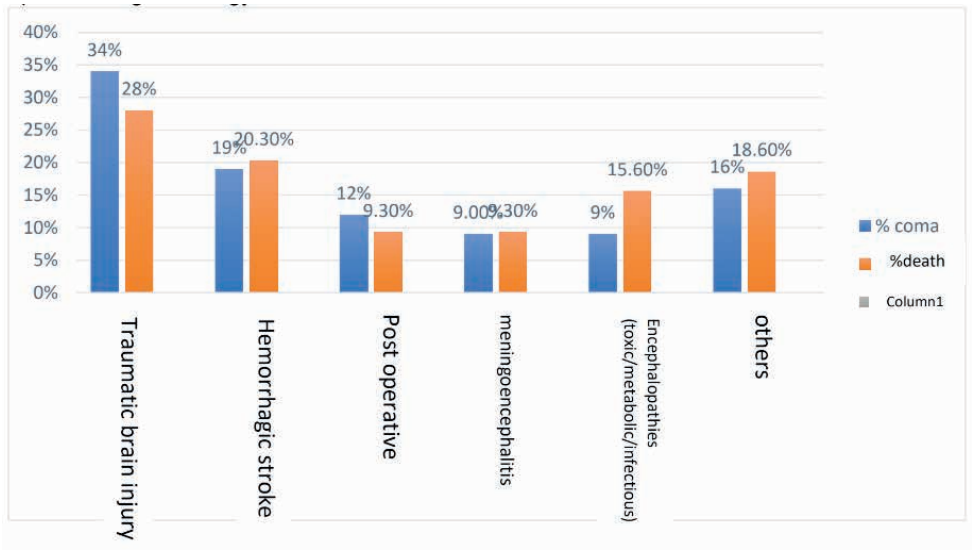
Data were descriptively analyzed using absolute and percentage frequencies, while Pearson's chi-square test was used to assess the significant association between electroencephalographic reactivity and the chance of regaining consciousness. The margin of error used in deciding the statistical tests was 5%.

RESULTS

EEGs of 132 patients were studied, of which 16 were excluded due to inconclusive information in the medical records regarding the final outcome, mostly due to transfer to another hospital in less than 2 months of follow-up.

Traumatic brain injury followed by hemorrhagic stroke accounted for more than 50% of the causes of coma in these 116 patients. Other causes of coma included postoperative meningoencephalitis, toxic, infectious and metabolic encephalopathies, ischemic stroke and cardiorespiratory arrest. After the 2-month follow-up of the patients, TBI was also the most common cause of death or coma (graph 1).

Of the total of 116 EEG recordings, 97 (83.6%) were reactive and 16 (16.5%) non-



Graph 1: Frequency of deaths and maintenance of the comatose state after 2 months of follow-up, according to etiology.

Reactivity in the electroencephalogram	Outcome								Value of p
	Death		Coma		Conscious		Total		
	n	%	n	%	n	%	n	%	
Reactive	47	48,5	5	5,2	45	46,4	97	100,0	$p^{(1)} = 0,001$*
Non-reactive	16	84,2	3	15,8	-	-	19	100,0	
Total group	**63**	**54,3**	**8**	**6,9**	**45**	**38,8**	**116**		

(*) Significant association to 5%

(1) Through Pearson's chi-square test.

Table 1 – Outcome according to the results of reactivity in the electroencephalogram

reactive. The percentages that died or remained in a coma were correspondingly higher among those with non-reactive EEG (84.2% x 48.5% of death and 15.8% x 5.2% in coma). While the percentage that regained consciousness was 46.4% among the EEG-R and was null among the non-reactive ones, $p < 0.01$ (Table 1). Therefore, 100% of patients with non-reactive EEG did not regain consciousness. Of the patients who remained without regaining consciousness, the limited follow-up of 2 months may have been insufficient to guarantee their real outcome.

DISCUSSION

The frequency, amplitude and reactivity of brain electrical activity have been demonstrated as predictors of improvement in coma. In the present study, electroencephalographic reactivity was not necessarily associated with recovery of consciousness, unlike what was demonstrated by Logi et al, 2011, in which of the 24 comatose patients with R-EEG, 22 of them recovered consciousness within 5 months after recording the EEG; while 26 patients had non-reactive EEG and 16 of them did not regain consciousness. The same was seen in the study by GangLiu et al, 2016, in which EEG reactivity was tested by applying somatosensory stimuli through evoked potentials in the right and left median nerves in 12 patients after CA. Of these, 7 patients with R-EEG, 6 had good results (PPV, 85.7%) and 4 of the 5 patients without R-EEG had unfavorable results (VPN, 80.0%).

As for the unfavorable outcome associated with non-reactivity in the EEG, this was seen by all authors, being corroborated by the present study. The absence of EEG-R has been reported with specificity between 70 and 100% as a predictor of poor prognosis, while for good prognosis the presence of EEG-R resulted in specificity of 55-95%. (Admiral, 2019)

The importance of electroencephalographic reactivity research has also been researched as a predictor of prognosis after cardiorespiratory arrest, proving to be a more sensitive method in the first 12 hours (non-reactive EEG with sensitivity of 57%) than absence of brainstem reflexes, and absence of N20 response in somatosensory evoked potentials (20-50% sensitivity). (Admiral, 2019)

The fact that in this study all the patients included were in a coma without the use of sedatives already demonstrates a greater severity of the clinical picture, which may have corroborated the poor outcome of almost half of the patients with EEG-R. The limited follow-up time (2 months) also raises the question whether a portion of these patients would later regain consciousness.

As for the stimulus performed, although there is no consensus, the use of different stimuli has been applied in different electroencephalogram centers, and the painful one has proven to be the most effective regardless of the method used to produce pain (Johnsen, 2018). Gutling et al, 1995, also tested EEG reactivity from somatosensory stimuli evoked in the mesdian nerve, in addition to auditory and painful stimuli, assuming that they could bring additional information since their pathways of afferent stimuli are different (medial leminisculum and formation ascending reticular, respectively). In addition, somatosensory stimuli are more resistant to the effect of sedation.

The analysis of electroencephalographic reactivity must be performed by a trained and experienced professional, and may be prone to subjectivity. (Hermansa, 2016). Even so, it is a simple, easy-to-perform, non-invasive and low-cost method that can provide valuable information regarding the prognosis of comatose patients, and must be performed in all electroencephalographic recordings of critically ill patients.

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