Serum prolactin levels in repetitive temporal epileptic seizures

A. SINISCALCHI1*, L. GALLELLI2*, N.B. MERCURI3, G. DE SARRO2

1Department of Neuroscience, Neurology Division, “Annunziata” Hospital, Cosenza (Italy)
2Chair of Pharmacology, Department of Experimental and Clinical Medicine, Faculty of Medicine, University Magna Grecia of Catanzaro, Clinical Pharmacology and Pharmacovigilance Unit, Mater Domini University Hospital, Catanzaro (Italy)
3IRCCS-S. Lucia and Department of Neurology, University “Tor Vergata”, Rome (Italy)

Abstract. – The primary aim of this work was: to evaluate the time course of serum prolactin (PRL) increase following repetitive seizures in epileptic patients with (Group II) and without (Group I) temporal ischemia.

Epileptic patients were examined after 2 or 3 epileptic seizures in wakefulness with seizure-free intervals of 4 hours. Serum PRL levels was assessed within 3 hours of the last epileptic seizure and up to 48 hours after.

The increase of serum PRL attained within baseline levels after 6 h in Group I and after 12 h in Group II. A longer increase of serum PRL levels were observed in Group II patients respect to Group I ($P < 0.01$).

In conclusion, this different long time attenuation of serum PRL following repetitive temporal seizures with and without damage of temporal structure, may be useful in order to better analyse the synaptic transmission involved in the pathways interconnect limbic areas.

Key Words:

Temporal lobe epilepsy, Repetitive seizures in wakefulness, Serum prolactin

Introduction

Prolactin (PRL) serum elevation following seizures has been considered a potential candidate for a surrogate marker1,2.

Pooled sensitivity was higher for generalized tonic-clonic seizures (60%) than for complex partial seizures (46.1%), while the pooled specificity was similar for both (approximately 96%)2.

*Siniscalchi A. and Gallelli L. share the authorship

Data were insufficient to establish validity for simple partial seizures. Usually, following an epileptic seizure the increase in serum PRL levels reached baseline levels within 6 hours. Therefore, serum PRL, when measured more than 6 hours after a suspected event, should be representative of the baseline PRL level (level B of recommendations)2. Inconclusive clinical studies in patients with repetitive seizure attacks, reported that the time between each seizure may be important to determine the serum PRL levels, even if the utility of serum PRL assay has not been established in the evaluation of single epileptic seizure and repetitive seizure2. However, there are not studies in repetitive temporal seizures, with and without damage of temporal structure, what they appraise the time attenuation of serum PRL.

The aim of our study was to evaluate the duration of serum PRL following repetitive seizures in wakefulness in patients affected by temporal lobe epilepsy with and without damage of temporal lobe.

Subjects and Methods

The study was performed in the Department of Neuroscience, Division of Neurology of Cosenza Hospital, Italy, in patients seeking Emergency Department care after seizures attacks in wakefulness.

Two groups of subjects were included in the investigation:

Group I (epileptic patients): patients with both an established diagnosis of temporal lobe epilepsy and repetitive partial seizures with secondarily generalized tonic-clonic seizures.

Group II (epileptic-ischemic patients): patients with cerebral ischemia in temporal lobe epilepsy and repetitive partial seizures with secondarily generalized tonic-clonic seizures.

*Corresponding Author: Luca Gallelli, MD; e-mail: luca_gallelli@hotmail.com
This study was approved by the local clinical Ethics Committee and patients signed written consent following explanation of the study.

The diagnosis of seizure was mainly performed on clinical criterions with the support of interictal electroencephalogram (EEG) with surface electrodes, magnetic resonance (MRI) and neuropsychological testing. Exclusion criteria were any metabolic and haemolytic disturbances, infective central nervous system diseases, endocrine conditions associated with hyperprolactinemia (i.e. prolactinomas, primary hypothyroidism history of traumatic brain injury), mesial sclerosis. Patients without detectable rise in PRL were excluded from our study; all patients were treated only with antiepileptic drugs in monotherapy or in add-on therapy, e.g. valproic acid, phenobarbital and carbamazepine. No other drugs able to increase the serum PRL levels were used in all groups. Patients with status epilepticus were also excluded from our study. From patients enrolled in this study, serum PRL was assessed within 3 hours after the last epileptic seizure in wakefulness. Blood samples for serum PRL concentrations were drawn from an antecubital vein. Serum PRL was evaluated 3, 6, 12, 18 and 24 h after the admission, always in wakefulness. In order to confirm the basal serum PRL levels, a blood sample was collected at 48 h. Aliquots were centrifuged and the serum separated and stored at –70°C until assayed. PRL concentrations were measured using a commercial radioimmunoassay method (Beckman Coulter S.p.A., Milan, Italy).

Statistical Analysis

Statistical analysis was performed by one way analysis of variance (ANOVA).

Results

In group I, we enrolled 5 males and 10 females (mean age = 56 ± 4 years) affected by established temporal lobe epilepsy. In group II we enrolled 4 males and 11 females (mean age = 59 ± 6 years) affected with ischemia in the temporal lobe and symptomatic temporal epileptic seizures. In both Group I and II, the seizures showed the same characteristic: secondary generalization tonic-clonic seizures with a focus in temporal lobe. In particular, in group I a focus in temporal right hemisphere was documented in nine patients, while in the left hemisphere for six others. In group II, temporal cerebral ischemia was documented in the right hemisphere in eleven patients and in the left hemisphere in four others.

Elisa test revealed high serum PRL levels about 3 hours from the last epileptic seizure in both group I and II (PRL serum levels: from 45.8 to 56.8 ng/mL and from 46.2 to 57.4 ng/mL, respectively; normal values 2.6-13.1 ng/mL). A decrease in PRL did not occur in both groups. No epileptic seizures were observed from last seizure during PRL sample collection.

A longer time course attenuation of serum PRL levels were observed in Group II respect to Group I ($P < 0.01$). In fact, serum PRL normalisation has been recorded not sooner than 6 hours in Group I (see Figure 1) and not sooner than 12 hours in Group II (see Figure 2).

Discussion

Many hypotheses exist about the mechanisms of basal PRL release. Usually, PRL release from the pituitary is tonically inhibited by the hypothalamus via dopamine, noradrenaline and gamma-amino-butyric acid release$^{3,4}$. In contrast, the release of PRL during seizures has not been well documented.

Experimental$^3$ and clinical$^{6,7}$ studies reported that ictal epileptic activity in the mesial temporal structures may propagate to the hypothalamus, and it is able to modulate the hypothalamic-pituitary regulation of PRL release. In patients with
medically intractable temporal lobe epilepsy, Lin et al. documented a normalization of serum prolactin (PRL) levels after lobectomy, suggesting that a seizure focus in mesial temporal structures play an excitatory role in PRL release.

Hyperprolactinemia has been described following a single generalized tonic-clonic, complex partial and, less frequently, simple partial seizures. PRL is released at the onset of generalized tonic-clonic or partial seizures, peaking within 15 to 20 min, and declining to baseline values by 60 min postictus. Recently, in 32 patients with postictal epileptic seizures, Willert et al. observed an increase in serum PRL levels up to 6 hours when compared with baseline PRL level. Meierkord et al. reported that seizure duration has no significant effect on PRL levels.

Inconclusive data exist regarding the value of serum PRL levels following repetitive or closely spaced seizures and few studies considered the time course of serum PRL levels attenuation following repetitive seizures. In repetitive epileptic seizure the seizure-free interval between each seizure may be important to determine the serum PRL levels. Using video-EEG, Malkowicz et al. observed that the post-ictal PRL rise was reduced when seizures occurred after short seizure-free intervals of less than 25 hours, compared with the levels of PRL occurring after longer seizure-free intervals. Conversely, another study showed that following repetitive seizures (mean 3 h and 32 min), post-ictal serum PRL levels were markedly and consistently increased in 5 of 14 patients studied, regardless of the time interval between seizures. None of the 14 patients showed a decrease in postictal PRL measure.

In our research, in both groups, we have observed an increase in PRL plasma levels, without significant difference between Group I and Group II. None of patients of both groups showed a decrease of post-ictal serum prolactin levels.

Kinson et al. reported that several drugs may be able to increase the plasma PRL levels. In our study, both Group I and Group II were treated only with anticonvulsant drugs (e.g. valproic acid, phenobarbital and carbamazepine). However, even if Bauer et al. documented that antiepileptic drugs may be able to moderately alter the PRL plasma levels, until now there are no data about the effects of these drugs on the duration of post-ictal prolactin levels.

Trimble hypothesized that the serum PRL increase 20 min after seizures is related to the neural stimulation of the limbic and other subcortical areas with subsequent spread of the epileptic discharges to the hypothalamic nuclei. More recently, it has been postulated that the excitatory synaptic glutamatergic transmission may be involved in the pathways interconnect limbic areas, particularly temporal lobe to the hypothalamus.

We observed an increase of serum PRL not sooner than 12 hours after the last seizure in epileptic-ischemic patients (Group II) respect to epileptic patients (Group I). However, we are not able to exclude that other pathological conditions (e.g. tumour, mesial sclerosis and other causes of damage of temporal structure), responsible for repetitive symptomatic temporal seizures, may induce a long time attenuation of serum PRL. Therefore, we hypothesize that this PRL long-time course may be due to an impairment in glutamatergic transmission from temporal lobe to hypothalamus that usually sustained inhibitory influence on PRL release.

In conclusion, since we cannot establish the role of serum PRL in the evaluation of repetitive seizures, our data may be useful in order to better analyse the synaptic transmission that may be involved in the intercourse between temporal lobe and hypothalamus. These pathways may be responsible of different time attenuation of serum PRL following repetitive temporal seizures with and without damage of temporal structure.


