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Serum prolactin levels after seizure and syncopal attacks

IVO LUŠIĆ*‖, IRENA PINTARIĆ*, IZET HOZO†, LOVRE BOIĆ‡ & VESNA ČAPKUN§

*Clinical Hospital Split, Department of Neurology, Spinčićeva 1, 21000 Split, Croatia; †Clinical Hospital Split, Department of Internal Medicine, Spinčićeva 1, 21000 Split, Croatia; ‡Clinical Hospital Split, Department of Ophtalmology, Spinčićeva 1, 21000 Split, Croatia; §Clinical Hospital Split, Department of Nuclear Medicine, Spinčićeva 1, 21000 Split, Croatia

Correspondence to: Ivo Lušić, MD., Ph.D., Clinical Hospital Split, Department of Neurology, Spinčićeva 1, 21000 Split, Croatia

Loss of consciousness and falling are the key features of syncope. Common accompaniments include tonic and myoclonic muscle activity, eye deviations, automatisms, vocalizations and hallucinations that may render the distinction from epileptic seizures difficult. The frequently increased levels of serum prolactin (SPRL) were observed immediately after generalized and complex partial seizures. Presumably, the hormone release is caused by the propagation of epileptic activity, usually from the temporal lobe to the hypothalamic pituitary axis. Numerous reports have demonstrated that the post-ictal SPRL level may be used to differentiate between epileptic and syncopal, non-epileptic attacks. In order to confirm the hypothesis, the SPRL levels were measured in patients with compex partial seizures (CPS) and patients with vaso-vagal syncopal attacks (VVS). The SPRL levels were prospectively measured for each patient as soon as possible after the event (within 1 hour), then 1 hour after the first determination and finally blood was sampled 24 hours later. During the study period (18 months), 18 patients with CPS and 15 patients with VVS were investigated in total. The mean values of SPRL levels in both groups were increased immediately after the event (CPS group: 1142 ± 305 mIU/l; VVS group: 874 ± 208 mIU/l). The elevated SPRL levels were found in 14 (78%) patients immediately after CPS and in 9 (60%) patients immediately after VVS. After examining the results of the present study we conclude that the elevated serum prolactin level after an epileptic attack is of no significant value in differential diagnosis between epileptic and vaso-vagal syncopal attacks.

Key words: prolactin; complex partial seizure; postural vaso-vagal syncope.

INTRODUCTION

Differential diagnosis between epileptic seizures, especially between complex partial seizures (CPS), pseudo-seizures and complicated syncope is a common diagnostic problem. The variety of ways in which seizures and syncopal attacks are expressed has made their diagnosis difficult, particularly because the patient frequently cannot describe either the nature or the duration of events. Investigations such as electroencephalogram (EEG) may aid diagnosis, but are never diagnostic in isolation. Reliance solely on EEG patterns can sometimes lead to both false positive, and false negative diagnoses.

Thus, the diagnosis of epilepsy on the basis of typical signs, symptoms, or routine laboratory tests is not an easy task. Diagnosis is further complicated by the close resemblance of some types of seizures to a variety of other neurological, psychiatric, and medical disorders.

‖ *E-mail*: ivo.lusic@st.tel.hr

Prolactin elevation has been described following generalized tonic–clonic and complex partial seizures[1–8]. Consequently, in the last few years, the determination of prolactin serum levels (SPRL), immediately after the attack, has been used as an ancillary investigation in differentiating between seizures and pseudo-seizures[2, 5, 8]. The same diagnostic clue was proposed for distinguishing between a seizure and complicated syncope[9–11]. To test this hypothesis, we examined the dynamics of serum prolactin concentrations after the epileptic attack and after postural vaso-vagal syncope.

MATERIALS AND METHODS

Patients were recruited from the population attending the Department of Neurology at the Clinical Hospital Split, seeking emergency treatment after unexpected syncopal attacks or after *grand mal* seizures. All pa-

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tients were admitted to the Department. Two groups of subjects were included in the investigation; those experiencing complex partial seizures and those experiencing vaso-vagal syncopal attacks (VVS):

CPS group: 18 female patients (mean age 28.2 ± 5.8 years), with an established diagnosis of epilepsy and seen immediately after a complex partial seizure attack. All patients were on medication (carbamazepine 14, valproic acid 6, metilphenobarbitone 3, lamotrigine 1, vigabatrin 1).

VVS group: 15 female patients (mean age 32.4 ± 5.5 years) examined immediately after typical postural vaso-vagal syncope attack, but otherwise healthy[12]. Those patients with a suspected or proven cardiac aetiology for syncope, or autonomic failure, were excluded from the study.

Dynamics of the serum prolactin concentrations were investigated as follows: serum prolactin levels were assessed as soon as possible after the event (fainting or seizure) — within 60 minutes following the episode ($SPRL_1$), then 60 minutes after the first sample was taken ($SPRL_2$), and the final determination of the prolactin level was made 24 hours later ($SPRL_3$).

Blood samples for serum prolactin concentrations were drawn from an antecubital vein. Aliquots were centrifuged and the serum separated and stored at $-60°C$ until assayed. Prolactin concentrations were measured using a commercial radioimmunoassay method (Prolactin-IRMA, manufactured by IBL, Hamburg, Germany). Values above 630 mIU/L (26 ng/ml) for women under 45 years were reported as elevated.

Statistical analysis: the Mann–Whitney U-test was used in order to compare unpaired samples because of the assumption that prolactin values were not normally distributed. The Wilcoxon test was used for comparing paired samples.

RESULTS

Figure 1 and Fig. 2 present the individual values of serum prolactin levels for the first two determinations ($SPRL_1$ and $SPRL_2$) in both groups of patients. In the CPS group $SPRL_1$ was elevated in 14 (78%) patients, and $SPRL_2$ was elevated in only 2 (11%) patients. In the VVS group $SPRL_1$ was elevated in 9 (60%) patients, and $SPRL_2$ in only 1 (6.5%) patient. In both of the groups, $SPRL_3$ remained within the normal reference range limits (under 630 mIU/l) in all patients.

Figure 3 presents the mean values of serum prolactin levels (MSPRL) in both groups of patients for each study period. There was an obvious higher mean serum prolactin level during the first sampling ($MSPRL_1$) in the CPS group in relation to the VVS group (Mann–Whitney test: $Z = 3.074$; $P = 0.002$), but mean serum prolactin values were elevated, compared with normal laboratory range, in both groups of patients. The differences in the mean serum prolactin levels between the CPS and the VVS group for the samples taken 1 hour ($MSPRL_2$), and 24 hours later ($MSPRL_3$), did not reach statistical significance (Mann–Whitney test: $MSPRL_2$ $-Z = 1.61$; $P = 0.11$; $MSPRL_3$ $-Z = 0.158$; $P = 0.17$). In both groups, there was a significant fall from $MSPRL_1$ values to $MSPRL_2$ values (Wilcoxon test: CPS group $-Z = 2.73$; $P = 0.006$; VVS group $-Z = 2.41$; $P = 0.012$).

DISCUSSION

A few disorders mimic epileptic seizures, especially complex partial seizures. We are often witness to 'seizures that do not look like seizures'. The most common imitators of seizures include syncope, cerebrovascular disorders, migraine, sleep and movement disorders, endocrine dysfunction, delirium, hyperventilation, dizziness, and vertigo. Clinical examination, physiological and biochemical tests can be used to differentiate the imitative conditions from epileptic seizures. Most of the features discussed raise important medical issues, because the urgency and course of treatment are quite different depending on the diagnosis. In addition to medical mimicry, malingering, episodic dyscontrol, psychogenic seizures, and pseudoseizures are also frequently misdiagnosed as epileptic seizures.

New insights into the phenomenology of syncope (transient cerebral hypoxia) have been gained from video analysis of experimentally induced syncope. Common elements of syncope include multifocal and generalized myoclonus, tonic body extension, automatisms, vocalizations, eye deviations and hallucinations[13–15]. Thus, it is not the presence or absence of these features but their specific character which distinguishes syncope from epileptic seizures. Other clues for differential diagnosis include precipitating factors, premonitory symptoms and post-ictal events, such as tongue bites and post-ictal confusion, which has been identified as the single most powerful factor discriminating syncope from epileptic seizures. In contrast, incontinence and head injury are common in both conditions. In rare cases, hypoxic and epileptic mechanisms may interact within one attack. Although a detailed history of an event may be helpful in most cases, the clinician often relies on ancillary test results to reach a diagnosis.

Serum levels of prolactin may increase as a consequence of some kind of epileptic seizures (*grand mal* and complex partial seizures), but the increase is transient. Usually, prolactin blood levels increase within 30 minutes post-ictally after epileptic seizures and return to normal values within 1 hour[4,5,7,8]. Seizure-

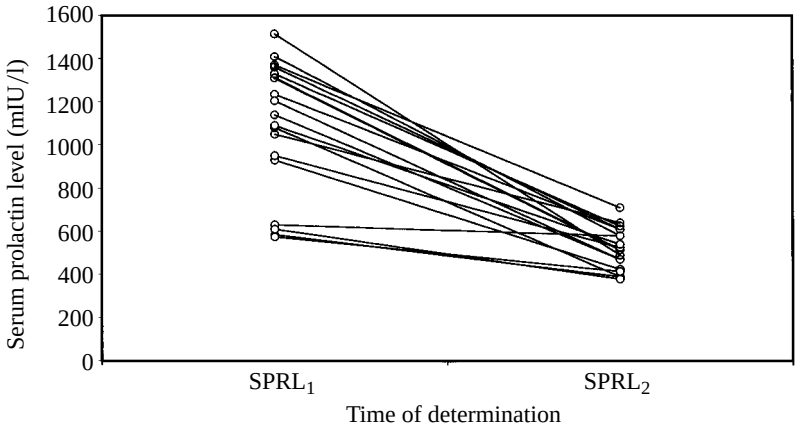

Fig. 1: Serum prolactin values (mIU/l) in patients with complex partial seizures ($n = 18$): immediately after the attack ($SPRL_1$) and 60 minutes later ($SPRL_2$).

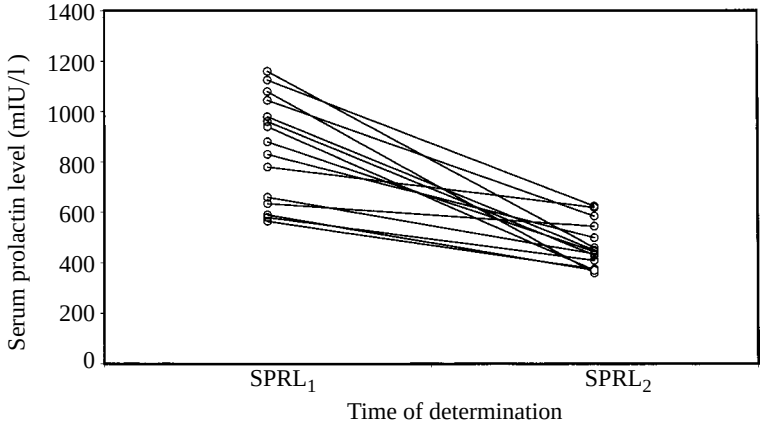

Fig. 2: Serum prolactin values (mIU/l) in patients with vaso-vagal syncope ($n = 15$): immediately after the attack ($SPRL_1$) and 60 minutes later ($SPRL_2$).

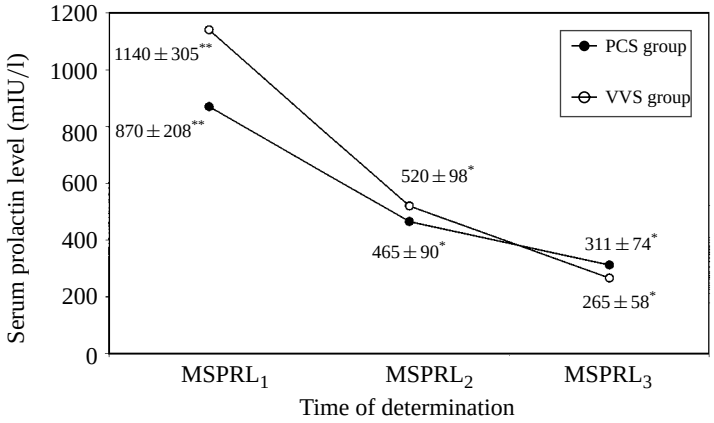

Fig. 3: Mean values of serum prolactin levels (MSPRL) in patients with complex partial seizure (CPS) and patients with vaso-vagal syncope (VVS) (mIU/l): $MSPRL_1$, values observed immediately after the attack; $MSPRL_2$, values observed 60 minutes after first determination; $MSPRL_3$, values observed 24 hours later. *P = NS; **$P = 0.002$.

free intervals should be considered when interpreting prolactin levels. After shorter seizure-free intervals, prolactin responses are reduced. This suggests that the amount of releasable prolactin is limited, depleted by seizures, or perhaps inhibited by prolactin feedback[7]. There is no significant influence of different antiepileptic drugs (sodium valproate, phenobarbital, carbamazepine) on serum prolactin levels[16].

The hormone release is caused by the propagation of epileptic activity, probably from the temporal lobe to the hypothalamic pituitary axis. Due to the intensity of the epilepsy after discharge, a rise in serum prolactin levels is seen, similar to that of 70% of complex partial seizures. Prolactin usually fails to rise after psychogenic seizures; therefore, post-ictal prolactin levels can be used to differentiate between epileptic and psychogenic seizures. However, a subclassification of epileptic seizures by means of prolactin measurement is not possible[11].

Prolactin levels are highly dependent on how quickly a blood sample is obtained after the event, the physiological severity of the event (localized or generalized in the brain), and the origin of the electrical discharge (e.g. frontal or temporal). The fact that prolactin levels often do not rise after seizures originating in the frontal lobes does not help to clarify these difficult-to-diagnose events. The lack of generalizability of such data prevents prolactin levels from being considered as a standard tool for diagnosis[15].

Numerous investigators have found that serum prolactin levels increase after tonic–clonic and complex partial seizures, but the effect of syncope on prolactin levels has been little studied. Several authors have reported that elevated serum prolactin levels could be useful in differentiating epileptic seizures from syncopal attacks[2, 3, 6, 8–11], but there are a few opposing conclusions[17–20].

The current study was conducted to test whether vaso-vagal syncope releases prolactin in serum, and also to investigate possible differences in serum prolactin dynamics between syncopal and epileptic attacks. The results obtained demonstrate that serum prolactin concentrations rise after vaso-vagal syncope, reaching a maximum within the first 60 minutes after an event. Consequently, our results do not support the theory that elevated prolactin levels could be helpful as an ancillary investigation in differentiating between epileptic (complex partial seizure) and vaso-vagal syncopal attacks. In our study, elevation of prolactin levels after the epileptic attacks was more robust than compared with the serum prolactin rise in patients with syncopal attacks, but this difference is insufficient to modify our conclusion about the usefulness of this test.

Patients with postural vaso-vagal syncope demonstrated numerous ‘exaggerated’ neurohumoral responses to syncope. Differential changes in plasma levels of epinephrine, renin, endothelin, vasopressin, cortisol, prolactin, beta-endorphins, and substance P have been reported by some investigators either prior to or during a syncopal episode in patients with vaso-vagal syncope. The precise pathophysiological significance of these measurements is unknown at the present time[21, 22].

CONCLUSIONS

Although the current study does not clarify whether it was the syncope itself, or the emotional stress (or both) that caused the prolactin elevations after syncopal attacks, it implies that measurement of this hormone will not help the clinician to distinguish between seizures and vaso-vagal syncopal attacks. Determination of serum prolactin can still be regarded as a valuable aid in the differential diagnosis between epileptic and psychogenic seizures.

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