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Serum Prolactin Concentrations and Epilepsy

A Study Which Compares Healthy Subjects with a Group of Patients in Presurgical Evaluation and Circadian Variations with Those Related to Seizures

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Summary. In 20 healthy subjects (10 female and 10 male) and 17 patients undergoing presurgical epilepsy evaluation with intracranial EEG electrodes, circadian variations of serum prolactin (PRL) were measured. A comparison between the peak values found in normals with the postictal rises in patients, led us to consider 700 μU/ml to be the threshold of diagnostic value and the observed rises above this level to be all induced by seizures. In order to asses the clinical value of this threshold, PRL was measured postictally in a further 30 patients with epilepsy and in 11 patients with psychogenic seizures. In none of the latter group did PRL rises exceed 700 μU/ml, while they did so in 39% of the complex partial seizures and in 80% of the tonic-clonic seizures. There was no significant difference with respect to sex (a rise over 700 μU/ml in 42% in male and in 55% in female patients). Based on the findings in 17 patients investigated by means of intracranial electrodes, we were not able to establish different criteria for different focus localisations: in 66% of both temporal as well as frontal lobe seizures the 700 μU/ml level was exceeded. As a trend, in the period preceeding an epileptic seizure we found a slightly decreasing PRL level, whereas in healthy persons the PRL concentrations gradually increased in the 40 minutes before the maximum spontaneous peak was reached.

Key words: Epilepsy – Prolactin – Psychogenic seizures – Differential diagnosis

Introduction

Increased serum prolactin (PRL) levels following spontaneous epileptic seizures were reported for the first time in 1978 (Trimble 1978). The incidence of these changes seems to depend on the type of seizure (Laxer et al. 1985, Bauer et al. 1987, Yerby et al. 1987, Johansson and von Knorring 1987, Bilo et al. 1988, Wroe et al. 1989), but they have never been observed following non-epileptic seizures (Collins et al. 1983, Pritchard et al. 1985, Bauer et al. 1987, Rao et al. 1989, Mishra et al. 1990). Not withstanding the numerous investigations carried out since 1978, a generally accepted definition of what can be regarded as a threshold of essentially increased postictal PRL levels in this regard has yet to be established. Former approaches have either been based on the comparison between post- and interictal measurements (Wyllie et al. 1984, Laxer et al. 1985, Sperling et al. 1986, Rao et al. 1989) or they defined a minimum threshold which, however, varied considerably between investigators (500–1000 μU/ml) (Oxley et al. 1981, Collins et al. 1983, Bauer et al. 1989). Moreover, in only some of the studies had the seizures investigated been documented by video-EEG-monitoring including intracranial electrodes (Laxer et al. 1985, Sperling et al. 1986) and only a few authors considered postictal elevation of PRL in the context of spontaneous fluctuations (Oxley et al. 1981, van Emde Boas et al. 1987).

The objective of our investigations was to establish a criterion or a set of criteria for evaluating postictal changes of PRL concentrations with regard to differential diagnosis. These criteria have to exclude the risk of false-positive finding after psychogenic seizures. Taking into account the physiological fluctuations in serum PRL levels (Sassin et al. 1972, Boyd and Reichlin 1978) we tried both to define a generally valid minimum threshold as well as a characteristic curve of the postictal rise. In addition it was hoped to observe a connection between the brain region of seizure onset and the likelihood of raised PRL levels.

Material and Methods

(a) In 20 healthy persons (10 female, mean age 24 year – range 22–31 – and 10 male, mean age 26 years – range 18–32 – circadian

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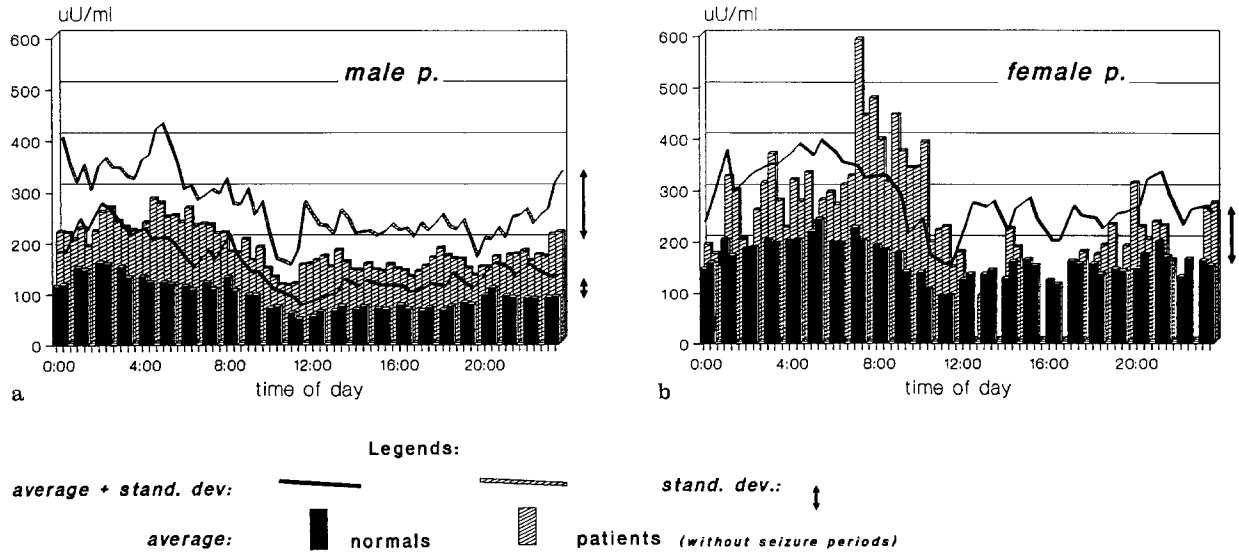

Fig. 1. Average circadian prolactin profiles in males (A) and females (B), seperate a healthy control group and the patients with epilepsy group. Bars represent mean values, lines represent means and standard deviations (standard deviation-values have not been calculated for female patients because their number was only 3; values sampled during seizures and two hours thereafter have been omitted)

serum PRL levels were measured. All the subjects were free of medication. None of the women was pregnant or taking the contraceptive pill. Blood (5 ml) was taken from an antecubital vein at 20 min. intervals over 24 h, stored at −20°C and analysed by a commercially available radio immuno assay. In all controls and patients the results of a combined stimulation test of the hypophysis (TSH, PRL, cortisol) were normal.

(b) 17 patients suffering from intractable focal epilepsies were investigated in the same way. Patient data, including antiepileptic drug therapy, are presented in table 1. All the drugs are known to have no or only slight influence on serum PRL concentrations (Wilson et al. 1979, Franceschi et al. 1984, Elwes et al. 1985, Bonuccelli et al. 1985 et 1986). 14 of these patients had sustained epileptic seizures during the period of investigation which were classified with the help of surface video-EEG monitoring and the additional use of sphenoidal, foramen ovale and/or subdural electrodes.

(c) In order to substantiate the idea regarding the discriminating power of the estimated threshold a further 30 in-patients (15 female, 15 male, mean age 34 years, range 19–62) were investigated during presurgical evaluation (the monitoring of these patients did not include the use of intracranial EEG electrodes). Blood was sampled within the first 5–10 minutes after a definite epileptic seizure had occurred.

(d) Another 11 patients (10 women, 1 man, mean age 31 years, range 22–52) suffered from psychogenic seizures; in this group, blood was taken once within 10 minutes after seizure onset. All of these seizures occurred during a state of wakefulness between 6:00 h and 22:00 h and mimicked tonic-clonic seizures. None of the patients was under anticonvulsant medication. PRL levels were measured as described above. To exclude endocrine disturbances PRL was measured in both groups (c and d) in the morning blood serum also. In all cases values were normal, i.e. lower than 500 μU/ml.

All of the clinical investigations of this study were performed at the Department of Neurology, University of Erlangen-Nürnberg. The informed consent of all persons was obtained before the investigations were carried out.

Aside from presenting examples of individual PRL profiles different procedures of descriptive statistics were applied.

(a) Mean circadian (i.e. 24 hours) profiles consist of the average values which were computed (together with the corresponding standard deviations) for every time of day (in steps of 20 min), excluding times of seizures and a 2-hour postictal period (see Fig. 1, below).

(b) Serum level-frequency histograms (i.e. the incidence of serum level-classes) characterize the over all-distribution of measured PRL values (i.e. averaged over time of day and subjects) in the subgroups (female and male, normals and patients) (see Fig. 2, below).

(c) Mean seizure related profiles consist of the average values computed for each time in certain temporal distances to the seizure onset (in steps of 20 min, starting 4 hours before and ending 4 hours after a seizure) omitting, of course, all periods of possible subsequent seizures (see Fig. 6, below).

Results

Figure 1 shows the mean circadian distribution of serum PRL in healthy persons and in patients with epilepsy (PRL levels measured during seizures and a 2-hour postictal period were omitted). It is obvious that the average values are higher in patients with epilepsy than in healthy persons. The night-peak is less prominent than that shown in other studies (Sassin et al. 1972); however, it has to be taken into account that none of the subjects in the present study had been able to maintain normal sleep during the investigation night. Hence, data sampled between 22:00 and 6:00 were not taken into consideration when searching for criteria to define seizure related rises. Figure 2 comprises the same data (all but seizure related values) in a time-independent form, i.e. as histograms. Both, Fig. 1 and Fig. 2 demonstrate that outside the seizures the value of 700 μU/ml had never been exceeded, either in healthy persons or in patients with epilepsy. This makes us take the value of 700 μU/ml as a threshold criterion for a definitely seizure-induced (i.e. 'postictal') PRL rise in wakefulness. From these data it would not

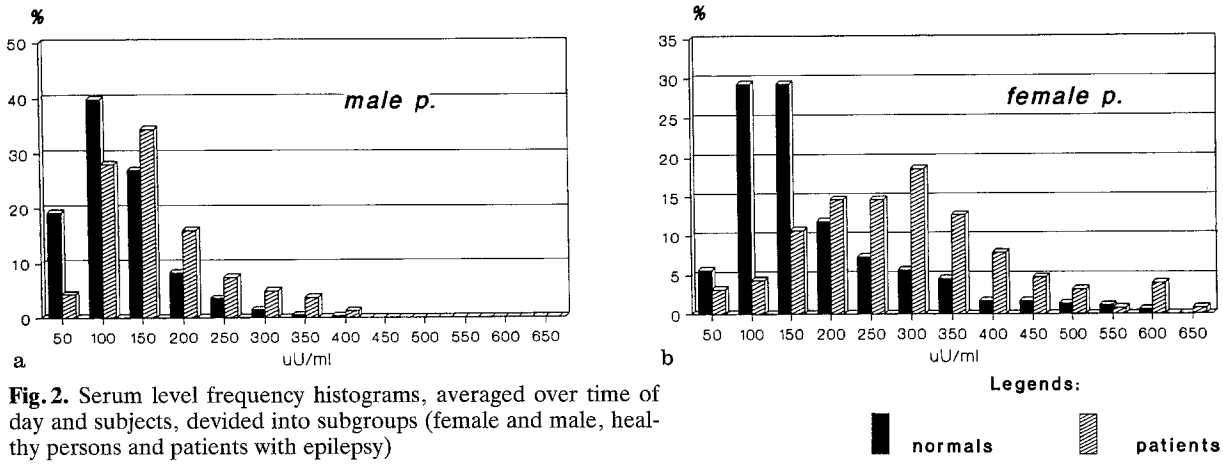

Fig. 2. Serum level frequency histograms, averaged over time of day and subjects, devided into subgroups (female and male, healthy persons and patients with epilepsy)

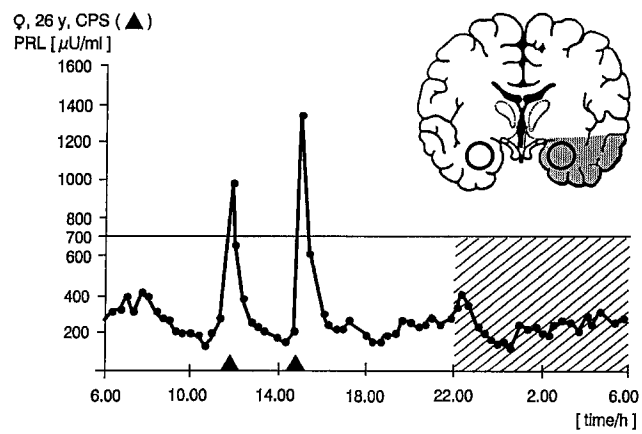

Fig. 3. Circadian PRL levels in a female patient (patient 1, table 1) with complex partial seizures (CPS; triangles). Following both seizures PRL was significantly increased above 700 μU/ml. The insert shows the EEG focus on the temporal left side

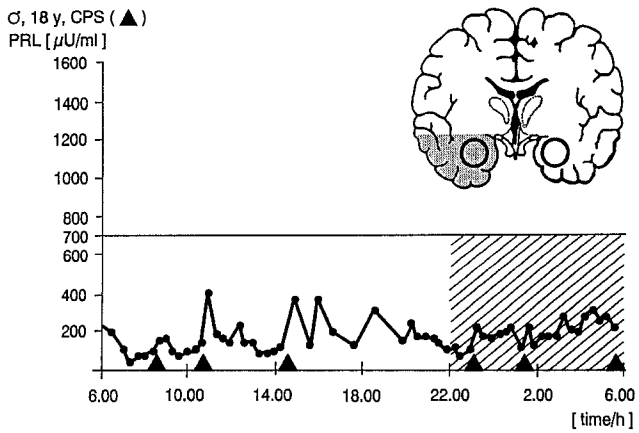

Fig. 4. Circadian PRL levels in a male patient (patient 6, table 1) with complex partial seizures (CPS, triangles). None of the six seizures was followed by a marked PRI rise. Only after two seizures (11.00 and 14.30) were there moderate peaks. The insert shows the EEG focus on the temporal right side

seem to be feasable to use differing criteria for males and females, particularly since for only 2 of the 26 male patients would a lower threshold have increased the sensitivity.

Presupposing 700 μU/ml to be an adequate criterion of seizure-induced PRL rise, it is by no means a necessary condition: in 52% of the investigated seizures this value was not reached. We therefore tested two theories of possible additional viewpoints to be applied in order to establish a set of criteria: First whether or not significant postictal PRL rises occur might depend on the anatomical region of seizure onset. Testing this theory had to be restricted to the group of 17 patients with implanted electrodes of whom 14 developed a seizure during the investigation period (Table 1). When dividing into subgroups according to different sites of seizure origin, the degree of significant rises is 6/9 (66%) for temporal, 0/2 (0%) for frontotemporal and 2/3 (66%) for frontal onset. Examples with significant rises, with moderate rises (i.e. below 700 μU/ml) and even with none at all are presented in Fig. 3 and 4.

Second, moderate peaks (below 700 μU/ml) were observed also in healthy persons (Fig. 5), otherwise the

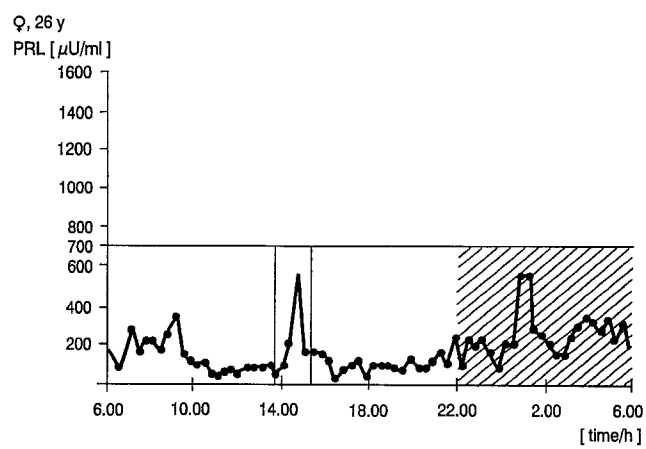

Fig. 5. Circadian PRL levels in a healthy, non-pregnant female. At 15.00 h a spontaneous PRL peak appeared. Cranial MRI and a combined stimulation test of the hypophysis were normal

threshold could have been defined on a lower level. This lead us to seek possible differentiating criteria other than the absolute peak value. Comparing the normalized peak related profiles gathered during seizures in epileptic patients with those measured and averaged in the course of

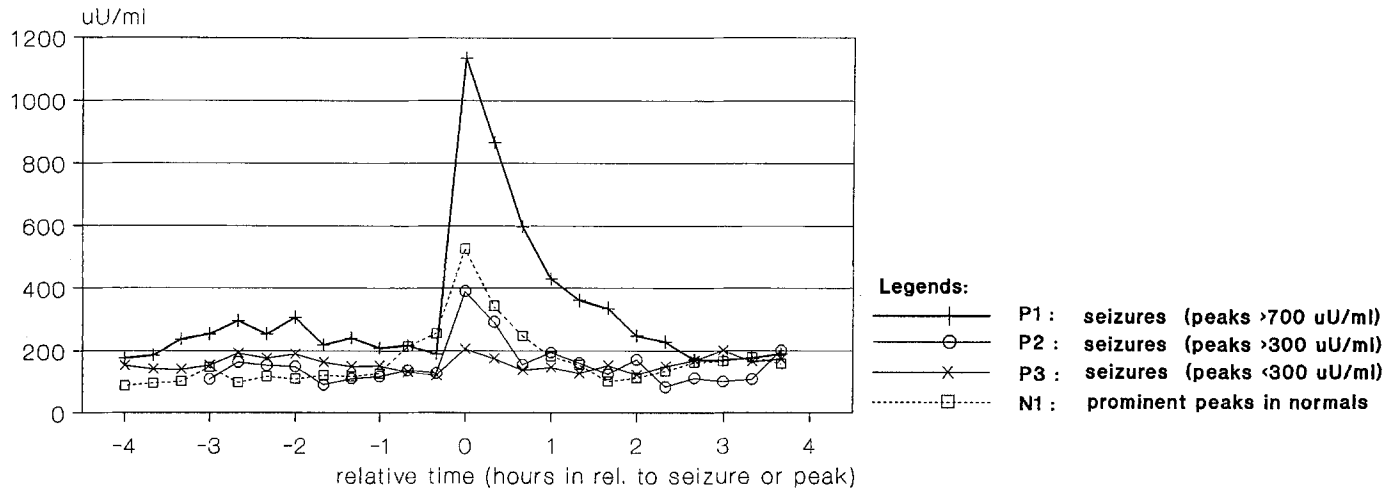

Fig. 6. Peak locked averages of serum prolactin levels; individual courses, beginning four hours before, ending four hours after the peak, were averaged using the time of peak levels as the trigger point (t = 0). Calculations were based on 15 seizures in 9 patients for P1, 7 seizures in 6 patients for P2, 22 seizures in 8 patients for P3 and 5 peaks in 3 healthy persons for N1

Table 1. Clinical data of the 17 patients with epilepsy investigated by means of intracranial electrodes. CPS = complex partial seizure; TCS = tonic-clonic seizure; f = female; m = male; sph = sphenoidale electrode; FO = foramen ovale electrode; OP = diagnosis based on histological investigations after surgery; MRI = diagnosis based on MRI investigations; CBZ = carbamazepine; VPA = valproate; Phb = phenobarbitone; + = significant increase of postictal serum PRL; − = absent postictal serum PRL increase above 700 µU/ml; 0 = no seizure during the investigation period

Pat.	Age, Sex	Seizure type	Seizure onset	Electrode position	Morphological findings	Medication	PRL
Seizures of temporal onset							
1	26, f	CPS	temporal left	scalp, sph, FO	gliosis (OP)	CBZ	+
2	31, f	CPS	temporal right	scalp, sph, FO	no path. findings (OP)	CBZ + VPA	+
3	22, f	CPS	temporal left	scalp, sph, FO	astrocytoma (OP)	CBZ + VPA	+
4	49, f	CPS	temporal right	scalp, sph, FO	gliosis temporal right (OP)	CBZ	0
5	26, m	CPS, TCS	temporal left	scalp, sph, FO	ganglioglioma (OP)	CBZ + VPA	−
6	18, m	CPS	temporal right	scalp, sph, FO	cyst (OP)	CBZ	−
7	26, m	CPS, TCS	temporal right	scalp, sph, FO	no path. findings (OP)	CBZ	−
8	21, m	TCS	bitemporal	subdural, FO	no path. findings (MRI)	CBZ + Phb	0
9	47, m	CPS	temporal left	scalp, sph, FO	gliosis temporal left (MRI)	CBZ + VPA	0
10	40, m	CPS	temporal left	subdural, FO	no path. findings (MRI)	CBZ + VPA	+
11	53, m	TCS	temporal right	scalp, sph, FO	gliosis temporal right (MRI)	Phb	+
12	43, m	CPS	temporal left	scalp, sph, FO	no path. findings (MRI)	CBZ	+
Seizures of fronto-temporal onset							
13	32, m	CPS, TCS	fronto-temporal	scalp, sph, FO	no path. findings (MRI)	Phb + VPA	−
14	43, m	CPS	fronto-temporal	subdural, FO	gliosis frontal right (MRI)	CBZ + VPA	−
Seizures of frontal onset							
15	23, m	tonic seizure	frontal right	scalp, sph, FO	cyst temporal right (MRI)	CBZ + Phb	−
16	19, m	TCS	frontal right	subdural, FO	no path. findings (MRI)	CBZ + VPA	+
17	27, m	TCS	frontal left	subdural, FO	no path. findings (MRI)	CBZ	+

peak rises in healthy controls, the latter do not show the slight preictal decrease (40 min before seizures start) which characterises the seizure related average profile (Fig. 6). This observation, however, represents only a hint; the figures are not adequate for establishing a statistical significance.

Summing up the results of PRL determination in all patients investigated (only the seizure with maximum rise was taken into account in patients under continuous recording, Table 1) the following was demonstrated: In 11 of 26 men (42%) and in 10 of 18 women (55%) PRL exceeded 700 µU/ml. In relation to seizure types, the positive rate was 13/33 (39%) in complex partial seizures, 8/10 (80%) in tonic-clonic seizures and 0/1 (0%) in a patient with tonic seizures. In the course of psychogenic seizures postictal PRL rises never exceeded 500 µU/ml, and the maximum for the only male patient was 235 µU/ml.

Discussion

The measurement of postictal serum PRL has been proved to be a useful tool in the differential diagnosis between epileptic and psychogenic seizures (Collins et al. 1983, Pritchard et al. 1985, Bauer et al. 1987, Rao et al. 1989). In spite of this, the criteria for judging postictal PRL concentrations used in various studies differ greatly. Rarely do they take into consideration the circadian fluctuation and interindividual variability of physiological PRL values (Oxley et al. 1981, van Emde Boas et al. 1987). The results of our study clearly reflect circadian variations. As is well known, PRL concentrations are generally higher in women than in men, higher during sleep than during wakefulness, and higher in patients with epilepsy than in healthy persons (Boyd and Reichlin 1978, Molaie et al. 1985 et 1987). The third of these facts seems to be related to interictal epileptic discharges inducing a low, but detectable rise of PRL secretion (Molaie et al. 1986). On the other hand, the influence of antiepileptic drugs in this regard, seems to be small and neglegible (Wilson et al. 1979, Franceschi et al. 1984, Elwes et al. 1985, Bonuccelli et al. 1985 et 1986). Since the conditions of our study would not allow the subjects' undisturbed night sleep, we are not able to draw conclusions with respect to nocturnal or sleep-related PRL rises. Within these limits, i.e. restricted to diurnal variations outside epileptic seizures, PRL concentration not once reached 700 μU/ml; in male persons the maximum even was below 450 μU/ml. Despite this remarkable phenomenon (which obviously is a direct consequence of the different physiological PRL levels in men and women), the relatively low number of subjects in the present study let us assume 700 μU/ml to be the decisive criterion for both males and females indicating a postictal rise after epileptic events; in only 2 of 26 male patients a lower threshold (450 μU/ml, if adopted separately for the male group) would have increased the sensitivity. As a future study, based on a larger number of patients investigated, it might be possible to identify sexspecific thresholds with greater accuracy.

The idea that the relative PRL increase might be a more suitable criterion than an absolute one, was not substantiated by our study. In healthy persons the relative increase was at times (Fig. 5) more prominent than that found after a number of seizure-related rises with peaks below 700 μU/ml (Fig. 4).

There is another interesting aspect when considering the curve of seizure-related percentage PRL changes: We found a gentle decrease of PRL levels in the period of 40 min before the seizure started; this was in contrast to what happened when relatively high peaks occurred in healthy persons (Fig. 6).

The disconcerting factor when defining 700 μU/ml as a criterion is the large number of false negative events, i.e. the fact that 23 of 44 (52%) seizures were not accompanied by a characteristic PRL rise. This was although all patients of our study had well defined epileptic seizures which were clinically and electroencephalographically exactly classified (with intracranial electrodes in 17 patients), and although the seizures under investigation were neither abortive nor particularly short lasting. The following factors are considered to contribute to the inadequate specifity of the criterion: Nonspecific postictal PRL rises were primarily observed in men who happened to be in the majority in our patient group. As discussed before, this might be related to the well known observation of higher mean PRL concentrations in women under physiological conditions (Boyd and Reichlin 1978). However, even in women postictal PRL rises have not in all cases exceeded 700 μU/ml (Hammers 1990, Bauer et al. 1990).

There are findings which suggest that individual factors influence the amount of PRL rise: whether or not postictal rises exceed the 700 μU/ml is intraindividually much more constant (e.g. patient 6 and 14, Table 1, always below; patients 1, 3, 10, 16, Table 1, always above) than interindividually.

In the present study patients with complex partial seizures (n = 33) prevailed over those with tonic-clonic seizures (n = 10). As in other studies too, we observed a lower rate of positive rises in the former type of seizures (39%) than in the latter (80%) (Wyllie et al. 1984, Yerby et al. 1987, Wroe et al. 1989, Fisher et al. 1991).

While there is a tendency to respond with a nearly identical PRL rise after repeated but isolated seizures the situation during status epilepticus (SE) is different: thus Tomson et al. (1989) did not find increased PRL levels in 15 cases at the end of SE. This is in contrast to our own findings in patient 2 (Table 1). Here PRL was measured in the course of SE with complex partial seizures, showing gradually decreasing amplitudes of the postictal serum PRL peaks. This led us to suppose that the PRL response was exhausted during SE (Bauer et al. 1992). Hence, the method of PRL measurement with the aim of a differential diagnosis between epileptic and psychogenic SE is a sensitive tool only if applied during the onset of the status.

Other factors conjectured to influence the postictal PRL rise are the level of intensity and localisation of the epileptic activity during the seizure. In both animal experiments and in presurgical stimulation tests in men, PRL rises were induced by electrical stimulations in the hippocampus (Parra et al. 1980, Sperling and Wilson 1986, Gallagher et al. 1987). Here, increase of PRL turned out to depend on the localisation and the duration of afterdischarges. The latter aspect seems to be of no relevance for the interpretation of our cases of absent rise because only seizures with significant ictal EEG changes lasting for a minimum of 1 min were taken into account.

Concerning the question of a possible relationship between PRL rises and focus localisation, it is well understood that temporal lobe seizures produce a PRL increase. Epileptic activation, generated in or propagating to the hippocampal area, spreads via the stria terminalis to the hypothalamus and induces an inhibition of the nuclei arcuatus and ventromedialis which both are known to decrease PRL secretion (Parra et al. 1980, Sperling and Wilson 1986, Bauer et al. 1989). This propagation pathway has been documented in animal experiments (Renaud 1976). In our study only 6 of 11 seizures (pa-

tients 1–14, Table 1) were accompanied by a marked PRL rise, although in all of them temporo-mesial brain structures had been involved (identified by means of foramen ovale electrodes).

Sperling et al. 1986 in a study in 78 patients with bilateral intracerebral electrodes found all 38 cases of bilateral limbic discharges accompanied by PRL rises, and also in 8 of 10 simple partial seizures with unilateral high frequent regional limbic bursts. All of the simple partial seizures showing other patterns of discharges or not involving limbic structures, did not produce PRL rises. Hence, complex partial seizures without PRL rise seem to involve predominantly extralimbic structures. This can not be verified by the present results however, since our study did not include intracerebral recording.

In regards to frontal lobe seizures, it is controversial whether they are able to induce PRL rises at all (Hammers 1990). In previous case reports (Bauer et al. 1991) we already have pointed out that a rise is a possibility. Also in the present study, 2 of 3 patients with frontal lobe seizures (patients 15–17, Table 1) demonstrated significant PRL rise. An anatomical interpretation, however, is less evident than it is for temporal seizures. Once it is assumed that a frontal onset propagates to the temporal lobe, the interpretation (including hippocampal structures) is as before. However, for this hypothesis fronto-cortico-(hypo)thalamic pathways have to be assumed to induce PRL rises. On the other hand, the lack of PRL increase may be interpreted by the assumption of epileptic activity restricted to the frontal lobe without propagation to temporal and hypothalamic structures (Geier et al. 1977, Williamson and Spencer 1986).

In summary, not withstanding invasive diagnostics and subtle seizure classification, the results of our study provide no unequivocal explanation why PRL in some patients does increase significantly and in others it does not. From the reverse point of view, this does also mean that PRL measurement is not helpful in classifying subtypes of partial epileptic seizures: no consistent difference was found betwen frontal lobe and temporal lobe seizures.

At present the 700 μU/ml threshold seems the best documented criterion in order to prove the epileptic nature of a seizure by means of PRL measurements; we determined this value unlike other studies, on the basis of closely spaced circadian serum level measurements in healthy subjects reflecting the physiological variation of this hormone, as well as in patients who sustained precisely classified seizures within the blood sampling period. Moreover, we were able to show that this threshold also was never exceeded in a further group of 11 patients suffering from psychogenic seizures. Finally we observed a slight decrease of PRL preceeding epileptic seizures in contrast to spontaneous peaks occurring in healthy persons. As mentioned above, for future studies it might be profitable to define a sexdependent threshold, which could be somewhat more specific.

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