Prolactin in the diagnosis of epilepsy

P. THARYAN, K. KURUVILLA, S. PRABHAKAR

ABSTRACT
The clinical differentiation of epileptic seizures from hysterical pseudo-epileptic seizures is sometimes difficult. The routine inter-ictal electroencephalogram is of limited use in such instances and prolonged electrophysiological monitoring for the detection of ictal changes may not always be feasible, especially in many centres in developing countries. This article focuses on hyperprolactinaemia as a biochemical marker of a recent ictus. It reviews studies that have explored the possibility of utilizing transient post-ictal elevations in serum prolactin as a diagnostic test in aiding the differentiation of epilepsy from hysterical pseudo-epileptic seizures. In the past decade many reports have documented post-ictal elevations in serum prolactin after tonic-clonic and complex partial seizures. Peak prolactin levels were observed 15 to 20 minutes after the ictus and values fell towards baseline within the hour. Evidence from these studies indicates that post-ictal hyperprolactinaemia is caused by involvement of medial temporal structures, especially the amygdala and hippocampus, by ictal discharges and the resultant disruption of tonic dopaminergic inhibition of prolactin release and/or stimulation of serotonin, rather than due to non-specific influences. The factors that affect the specificity, sensitivity and predictive value of post-ictal hyperprolactinaemia as a diagnostic test are discussed and a standard test procedure and definition of test result proposed that would improve its clinical utility. The test is recommended as a simple, relatively inexpensive, highly specific and fairly sensitive aid to diagnosis.

INTRODUCTION
The diagnosis of epilepsy is essentially clinical. In the differential diagnosis of paroxysmal non-epileptic conditions mistaken for epilepsy, pseudo-epileptic seizures pose special problems and are a common manifestation of hysteria particularly in developing countries. Although numerous features have been compiled to distinguish pseudo-epileptic seizures from epilepsy, it is still not possible to make this distinction with certainty. In one study, the accuracy of clinical diagnosis ranged from 60% (for physicians referring patients for evaluation) to 72% (for neurologists viewing video-taped analyses of seizures, without knowledge of the clinical details or the accompanying electroencephalogram). The greatest difficulty in diagnosis is caused by complex partial seizures. Additional difficulties are caused by the co-existence of pseudo-epileptic seizures in 12% to 65% of patients with a past or a concurrent history of epilepsy. The inter-ictal scalp electroencephalogram (EEG) is routinely used to confirm the diagnosis of epilepsy. However, since a normal inter-ictal EEG is found in about 50% of patients with epilepsy, it is of limited use in unequivocally resolving the differential diagnosis between an epileptic and a pseudo-epileptic condition. It is also of no use in detecting pseudo-epileptic seizures in a known epileptic. The picture is confused by the observation that some non-epileptic, psychiatric patients show inter-ictal epileptiform EEG abnormalities.

The use of sphenoidal, nasopharyngeal and implanted depth electrodes (with or without special activation procedures) to increase the yield of inter-ictal EEG abnormalities, or the use of video telemetry and ambulatory cassette EEG to detect ictal events, leads to a greater diagnostic accuracy. These procedures are inconvenient, expensive and not available at most centres in developing countries. A biochemical marker of epileptic seizures would therefore be of considerable clinical use.

HYPERPROLACTINAEMIA
Based on the observation that electrical stimulation of the medial basal hypothalamus in rats increased prolactin release, Trimble investigated the hypothesis that, in epilepsy, abnormal electrical activity passing through the midbrain should elevate prolactin levels. He reported that serum prolactin concentrations rose significantly after generalized tonic-clonic seizures and after electroconvulsive therapy, but not after hysterical seizures or in patients with 'minor convulsions'. Later, others have confirmed that prolactin levels are significantly elevated after most generalized tonic-clonic and complex partial seizures, but not after most simple partial seizures. Myoclonic, atonic, and absence seizures or pseudo-epileptic seizures. Post-ictal prolactin elevations commenced at the onset of the seizure, peaked at 15 to 20 minutes after the seizure, and fell towards baseline levels by 1 hour. Seizures were diagnosed in accordance with the International classification, after clinically observed seizures, following seizures documented by ictal EEG recordings using videotelemetry, with or without sphenoidal or implanted intracerebral electrodes.
Physiology of prolactin

Prolactin is a polypeptide hormone which is synthesized, stored and secreted by the lactotrophs of the anterior pituitary. It has a half-life of 15 to 20 minutes and its turnover is rapid. Normal adult serum levels are 5 to 15 ng/ml in men and 5 to 25 ng/ml in women, the increase in the latter occurring at puberty. Prolactin levels decline after menopause and are 50% of adult levels after the age of 65 years. The various phases of the menstrual cycle do not significantly affect prolactin levels.33-35 During waking hours, there is a pulsatile release with no fixed periodicity, with a background of regular secretion. This pulsatile pattern is not only the result of the circadian organization, but is also related to sleep, including day-time naps. Nocturnal prolactin levels rise shortly after the onset of sleep, peak between 4 and 6 a.m., rarely exceeding 30 ng/ml and decline soon after awakening with the lowest levels being reached 1 to 3 hours later.36,37

Biochemical marker or artefact?

Prolactin elevations are seen most commonly during pregnancy and lactation, but also in a variety of pathological and pharmacological conditions (Table I). Stress of any sort increases prolactin and elevations can follow those seen after epileptic seizures are also seen after seizures induced during electroconvulsive therapy with,18,40-42 or without27 anaesthesia and muscle relaxation sufficient to prevent major convulsive movements. Such rises are not seen after anaesthesia alone40 or after sham ECT.41 Thus, the post-ictal prolactin surge is a biochemical marker of generalized tonic–clonic and complex partial seizures and of potential use in differentiating them from pseudo-epileptic seizures.

NEURONAL PATHWAYS INVOLVED IN POST-ICTAL HYPERPROLACTINAEMIA

Hypothalamus

Since the limbic portion of the temporal lobes is believed to be involved in the genesis of complex partial seizures of temporal lobe origin,43 and there are connections between medial temporal lobe structures and the hypothalamus, it has been suggested that involvement of these structures in the ictal discharge is responsible for the post-ictal prolactin surge.20,26,29 Simple partial, myoclonic, absence and atonic seizures do not generally elevate prolactin, presumably because medial temporal lobe involvement either does not occur, or is insufficient in intensity to cause prolactin release.

Medial temporal structures

The role of the amygdala and hippocampus in the post-ictal prolactin surge has been emphasized in studies where these structures have been electrically stimulated. Stimuli that led to a generalized tonic–clonic or complex partial seizure always resulted in post-ictal prolactin elevation, while stimuli that did not elicit an after discharge were not.44 Similarly, simple partial seizures originating from non-temporal sites did not evidence hyperprolactinaemia until secondary generalization occurred.26 Hyperprolactinaemia was observed in simple partial seizures with high frequency discharges widely involving limbic structures, hyperprolactinaemia was observed, whereas those with low frequency discharges or where widespread involvement of limbic structures was not evident, prolactin elevations did not occur.31 Complex partial seizures with only auras or behavioural arrests without motor automatisms did not elevate prolactin, irrespective of the duration of the seizure.26-31 Brief generalized tonic–clonic seizures (less than 30 seconds) were also not followed by hyperprolactinaemia.18,30 Subclinical seizure activity, manifested as paroxysmal bursts of epileptiform abnormalities on EEG without clinical evidence of seizures, was also not followed by prolactin elevation.45 These findings indicate that the intensity and spatial extent of medial temporal involvement in the ictal discharge is over baseline levels, while in complex partial seizures without convulsive components, peak post-ictal levels are 3 to 17 times greater than baseline values.27,28 Secondly, prolactin changes in stressed, nonepileptic subjects are negligible compared to post-ictal rises,19,27 and post-ictal changes in cortisol and growth hormone, other stress responsive hormones, do not produce prolactin-like changes.19,23,29 Finally, prolactin elevations similar to those seen after epileptic seizures are also seen after seizures induced during electroconvulsive therapy with,18,40-42 or without27 anaesthesia and muscle relaxation sufficient to prevent major convulsive movements. Such rises are not seen after anaesthesia alone40 or after sham ECT.41 Thus, the post-ictal prolactin surge is a biochemical marker of generalized tonic–clonic and complex partial seizures and of potential use in differentiating them from pseudo-epileptic seizures.

### Diseases associated with hyperprolactinaemia

- Hypothalamic disease
- Pituitary neoplasms, chromophobe adenoma
- Acromegaly
- Ectopic production—renal, bronchogenicca
- Hyperestrogenemia
- Liver disease, chronic alcoholism
- Renal failure
- Hypothyroidism
- Addison's disease

### Drugs elevating prolactin levels

- Antihypertensives—reserpine, methydopa
- Antipsychotics—phenothiazines, butyrophenones
- Tricyclic antidepressants—clomipramine
- Opiates—morphine, pethidine
- Oral contraceptives
- Protirelin
- Metoclopramide
- Cimetidine

### Drugs lowering prolactin levels

- Ergot derivatives
- Bromocriptine mesylate
- Levodopa
- Apomorphine
- Clonidine

### Table I. Conditions altering baseline prolactin levels

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crucial for prolactin release; seizure duration per se does not seem to influence prolactin release independent of these parameters.

Since the ventromedial hypothalamus receives excitatory projections from the amygdala, mainly via the ventral amygdalofugal pathway (Fig. 1), activation of this pathway by spreading ictal activity has been postulated to trigger prolactin release.

However, amygdalar involvement alone, without widespread involvement of the hippocampus and hippocampal gyrus, did not cause prolactin elevations, suggesting that the direct amygdalofugal pathway may not be important in post-ictal prolactin release. The amygdala and hippocampus may instead serve as 'triggers' of after discharges which are secondarily conducted to subcortical structures including the diencephalon, mesencephalic tegmentum and septal region. These structures then project to the hypothalamus and cause prolactin release.

NEUROCHEMICAL MECHANISMS INVOLVED IN POST-ICTAL HYPERPROLACTINAEMIA

Inhibitory influences

The neuro-endocrine regulation of prolactin secretion by the hypothalamus is predominantly a tonic inhibition, primarily by dopamine synthesized by tubero-infundibular dopaminergic neurons in the arcuate and paraventricular nuclei of the medial basal hypothalamus, and mediated by stereospecific dopamine receptors located on pituitary membranes, in particular those of lactotrophs. There also exists a short-loop feedback, possibly mediated by dopaminergic neurones, whereby high levels of prolactin increase the turnover of dopamine, thereby inhibiting further prolactin secretion. Thus, disruption of the tonic dopaminergic inhibition of prolactin by spread of seizure discharge is a postulated mechanism underlying post-ictal hyperprolactinaemia. The transient nature of the prolactin surge is possibly explained by the short half-life of prolactin as well as by the activation of the short loop feedback system (Fig. 1). However, a tubero-infundibular gamma aminobutyric acid (GABA)ergic system has also been described with high affinity GABA receptors on the pituitary membranes. While of uncertain physiological significance, it is possible that GABA could inhibit prolactin when prolactin levels are substantially elevated.

Stimulatory influences

Protirelin (synthetic Thyrotropin releasing hormone, TRH) is a potent stimulus for prolactin secretion and acts directly on TRH receptors on the lactotrophs. However, TRH seems unlikely to mediate post-ictal prolactin elevations as thyroid stimulating hormone (TSH) values were not significantly elevated after seizures. Moreover, a faster prolactin peak was seen after ECT than after intravenous TRH administration, suggesting that different mechanisms may operate in the two conditions. Vasoactive intestinal polypeptide and endogenous opioids stimulate prolactin release, and beta-endorphin concentrations increase rapidly after seizures. Endorphins decrease dopamine synthesis and release in the hypothalamus; it is hence possible that the post-ictal prolactin surge is opioid mediated. Serotonin is known to elevate prolactin levels and pretreatment with methysergide, a hydroxytryptamine 1 and 2 (5-HT1,5-HT2) receptor antagonist, blocked the electroconvulsive treatment (ECT) induced prolactin surge.

Thus, inhibition of dopaminergic tonic inhibition as well as stimulation of serotonin by the seizure discharge seem to underlie post-ictal hyperprolactinaemia (Fig. 1). The role of GABA and opioid peptides in this process requires further elucidation.

OTHER BIOCHEMICAL MARKERS OF EPILEPTIC SEIZURES

Investigations on post-ictal changes in cortisol, adrenocorticotropic hormone (ACTH), growth hormone and TSH after ECT and spontaneous seizures have not indicated the usefulness of these hormones as biochemical markers of epileptic seizures. After generalized tonic–clonic seizures, Follicle stimulating hormone (FSH) levels were significantly elevated at 20 minutes in female patients and luteinizing hormone (LH) levels were elevated even after 1 hour in both males and females. However, these gonadotropins were not elevated after complex partial seizures. Among posterior pituitary hormones, arginine vasopressin levels were inconsistently elevated immediately after some generalized tonic–clonic seizures. ECT stimulated elevations in plasma concentrations of both vasopressin associated neurophysin as well as oxytocin associated neurophysin, but since assays of neurophysins are specialized techniques and unlikely to
become widely available, neurophysins may not be of practical value as biochemical markers. Prolonged creatinine kinase elevations were reported after generalized tonic-clonic seizures, but only in 15% of patients, and not after other seizure types. Thus, to date, hyperprolactinaemia is the only consistently reported biochemical marker of an epileptic seizure of any practical significance as an aid to diagnosis.

CLINICAL UTILITY OF POST-ICTAL HYPERPROLACTINAEMIA

The clinical utility of any biochemical test is determined by its sensitivity, specificity and predictive value, apart from practical and economic considerations. Pooling the results of 12 published studies, the sensitivity of post-ictal hyperprolactinaemia has been estimated to be 63% and the specificity 91%. However, this estimate is likely to be misleading due to differences in the studies in various aspects of test performances.

Definition of hyperprolactinaemia

The initial definition of hyperprolactinaemia was based on arbitrarily defined absolute increases of peak prolactin levels above 1000 IU/L (>45 ng/ml) for generalized tonic-clonic seizures and above 500 IU/L (>36 ng/ml) for complex partial seizures, yielding false-negative results in 4% to 40% of the former and 22% to 37% of the latter. Some workers have used statistical analysis to compare prolactin increases of at least twice to three times24.27.28 baseline values as indicative of genuine epilepsy with 100% specificity and sensitivity ranging from 43% to 100% for complex partial seizures and 80% to 100% for generalized tonic-clonic seizures.

Timing of samples

The sensitivity and specificity of the test are also influenced by the timing of post-ictal prolactin samples. Peak prolactin values are obtained 15 to 20 minutes after seizures; however, the prolactin peak may occur later than 15 minutes in some patients. Hence, the preferred time for sampling peak post-ictal prolactin elevations may be 20 minutes after the event. Baseline samples are often obtained 60 minutes after the ictus and a fall in prolactin levels towards baseline values is taken as an additional indicator of genuine epilepsy. However, prolactin levels may still be elevated 60 minutes after the seizure, especially in patients with very high peak elevations. The 60-minute sample would therefore not detect those patients with elevated baseline values. Since prolactin release is pulsatile, pooled baseline samples are recommended. However, a single baseline sample taken 24 hours after the event, to control for circadian variations, is reasonably accurate, more practical and preferable to a 60-minute sample. Baseline prolactin values in epileptic subjects even on anticonvulsant medication are usually within normal limits, though in some cases, hyperprolactinaemia may occur. In subjects with elevated baseline prolactin values, post-ictal hyperprolactinaemia does occur, but the magnitude of elevations is variable (unpublished observations); hence the proposed cut-off values may not apply. Table II summarizes the details of the test procedure that would enable optimal clinical use.

False-negative results

Hyperprolactinaemia may not be evident after genuine epileptic seizures during status epilepticus, presumably owing to depletion of stored prolactin by the preceding attacks or due to activation of the dopaminergic system by repeated seizures. The magnitude of prolactin elevations may be diminished in elderly people above the age of 65 years and in prepubertal children, presumably caused by decreased prolactin reserves. Prolactin changes after seizures occurring during sleep, where baseline values are likely to be elevated, have not been adequately studied.

False-positive results

In the presence of normal baseline values, prolactin levels greater than three times baseline values, do not, as a rule, occur after pseudo-epileptic seizures, attesting to a high specificity to the test. Hence, behaviour classified as pseudoseizures, if followed by peak post-event prolactin elevations greater than three times baseline levels, warrants further evaluation to rule out underlying seizure activity. The ability of hyperprolactinaemia to differentiate epilepsy from paroxysmal non-epileptic conditions other than pseudoseizures has not been adequately documented. Syncope attacks, especially 'convulsive syncope', may be accompanied by hyperprolactinaemia, hence prolactin changes after paroxysmal ischaemic events need further study.

Predictive value

The predictive value of any test refers to the probability that a particular result will accurately diagnose the condition in a particular patient and is a function of the prevalence of the disorder in question. Thus the predictive value of post-ictal hyperprolactinaemia in the differentia-

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### Table II. Details of test procedure

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<th>Collection of blood samples</th>
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<tr>
<td>Insert iv line with heparin lock at cessation of seizure</td>
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<td>1st sample 20 minutes after seizure</td>
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<tr>
<td>2nd sample 60 minutes after seizure (optional)</td>
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<tr>
<td>Baseline sample 2+ hours after seizure (ensure 2-4 hours free period prior to this)</td>
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<td>Separate serum, store at -20 degree C till assay</td>
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<th>Interpretation of results</th>
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<td>(a) Preferred methods</td>
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<td>Positive if 20 minute prolactin value is abnormally elevated and greater than three times the 24 hour prolactin value (latter should be within normal limits).</td>
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<td>(b) Useful if 24 hours sample is not obtainable</td>
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<td>Also positive if 20 minute prolactin value is greater than 500 IU/ml (&gt;36 ng/ml) and 60 minute value near or within normal limits.</td>
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tion of pseudoseizures from genuine seizures will be greater in settings where the prevalence of pseudoseizures is high, e.g. neurological and psychiatric tertiary care settings. A thorough understanding of the factors affecting the sensitivity and specificity of the test will restrict its use to situations where the test results are likely to accurately reflect the underlying condition and will increase its clinical utility.

**Practical limitations**

While the test has clear economic advantages over intensive electrophysiological investigations, practical limitations may further restrict its clinical utility. Radioimmunoassay of prolactin is a relatively simple procedure, but it may not always be available. Prolactin assays are done in batches and the resultant delay in obtaining results, in centres where prolactin assays are not commonly done, would be a disadvantage. Difficulty in timing with precision the termination of complex partial seizures clinically, may make timing of peak prolactin elevations erroneous. The transient nature of the prolactin surge would also necessitate in-patient monitoring to detect ictal events and in patients with infrequent seizures, such monitoring may be impractical. It is hence recommended that estimation of post-ictal prolactin levels be restricted to patients with a high frequency of seizures where diagnostic differentiation between epilepsy and pseudoseizures is difficult, especially in patients suspected to have combinations of the two conditions. Prolactin changes would then, especially in the latter instance, aid diagnostic differentiation.

**CONCLUSIONS**

Transient elevations in serum prolactin greater than three times baseline values are seen 20 minutes after most generalized tonic-clonic seizures and complex partial seizures. Estimations of prolactin at this time would enable differentiation of such events from hysterical pseudo-epileptic seizures where prolactin changes are negligible. Post-ictal hyperprolactinaemia is a biochemical marker of these epileptic seizures and results from neuronal and neurochemical changes caused by spread of seizure discharge through limbic structures. A thorough knowledge of the factors affecting the sensitivity and specificity, and the practical limitations of hyperprolactinaemia as a diagnostic test would ensure its proper application and increase its clinical utility. It is recommended as an aid to clinical diagnosis in situations where a differentiation between epilepsy and hysterical pseudo-epileptic seizures is not possible on clinical grounds alone, or by electrophysiological means, especially in patients with a combination of the two conditions.

**REFERENCES**


