

SERUM PROLACTIN CHANGES IN EPILEPSY AND HYSTERIA

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SUMMARY

The usefulness of post-ictal serum prolactin changes, as an adjunct, in the differentiation of generalized tonic-clonic seizures and complex partial seizures from hysterical pseudoepileptic seizures, was investigated in a double blind study designed to control for variables known to alter prolactin levels. Significant post-ictal hyperprolactinemia, with a peak at 20 minutes and a fall towards baseline by 1 hour, was found after complex partial seizures, generalized tonic-clonic seizures and after bilateral, unmodified ECT, but not after hysterical pseudoepileptic seizures or in stressed, non-epileptic controls. A proportionate increase in peak prolactin levels of at least thrice baseline values was found to best differentiate genuine seizures from pseudoepileptic seizures. Postictal hyperprolactinemia is a sensitive biochemical marker of a genuine seizure and of potential use in the differentiation of epileptic from hysterical pseudoepileptic seizures.

Introduction

The differentiation between epilepsy and hysterical pseudoepileptic seizures is generally possible on clinical grounds. Difficulties in making this differentiation do occur, especially in the case of complex partial seizures, where the bizarre and myriad presentations often prompt the diagnosis of hysteria, even by experienced clinicians. Adding to the diagnostic dilemma in 12-65% of cases, is the paradoxical coexistence of genuine epilepsy and pseudoepileptic seizures in the same patient (Fenton 1986).

The use of implanted depth electrodes, videotelemetry, and ambulatory EEG monitoring enables a greater degree of diagnostic accuracy than is possible with the routine interictal scalp EEG; however, the expenses and inconvenience involved precludes the widespread use of such procedures. A biochemical marker of an epileptic seizure would therefore be very useful.

Over the past decade, transient post-ictal hyperprolactinemia, with a peak occurring between 15-20 minutes postictally and a fall towards baseline levels by 1 hour, has been consistently reported after ECT (Ohman et al. 1976; Deakin et al. 1983), and less consistently after generalized tonic-clonic seizures and complex partial seizures, but not after simple partial seizures, myoclonic seizures, atonic seizures or pseudoepileptic seizures of hysterical origin (Trimble 1978; Abbott et al. 1980; Dana-Haeri et al. 1983; Collins et al. 1983; Wyllie et al. 1984; Bye et al. 1985; Pritchard et al. 1983 & 1985; Laxer et al. 1985).

Trimble's group (Dana-Haeri et al. 1983) proposed that a prolactin value 20 minutes after a generalized tonic-clonic seizure of more than 30 seconds duration, of 1000 mU/ml or more, and 500 mU/ml or more after complex partial seizures, would differentiate such cases from hysterical pseudoepileptic seizures. Further confirmation, they added, could be obtained by an addi-

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tional sample at 60 minutes, demonstrating a fall towards baseline levels. However, using these arbitrarily defined cut off levels, 4-40% of generalized tonic-clonic seizures and 22-37% of complex partial seizures were wrongly classified (Dana-Haeri et al. 1983; Trimble 1986). Moreover, patients with elevated baseline prolactin values would not be detected when only a 20 minute and 1 hour sample are used.

The aims of the present study were to

- a) study postictal prolactin changes after a clinically observed seizure, in patients with generalized tonic-clonic seizures, complex partial seizures, patients undergoing ECT and patients with hysterical pseudoepileptic seizures, using a control group of stressed, non-epileptic patients.
- b) attempt to establish cut off levels in the magnitude of post-ictal prolactin changes that would best differentiate hysterical pseudoepileptic seizures from generalized tonic-clonic seizures and complex partial seizures.

Material and Methods

Serial prolactin estimations were done after a clinically observed seizure in 13 patients with epilepsy (8 with complex partial seizures and 5 with generalized tonic-clonic seizures), 15 patients who underwent bilateral, unmodified ECT for the treatment of endogenous depression, and 11 patients with hysterical pseudoepileptic seizures. Fifteen, age and sex matched, non-epileptic patients with acute medical and surgical illnesses served as controls.

For all patients in the study, a detailed clinical history, physical examination and relevant investigations were performed to rule out any physical illness known to be associated with altered prolactin levels.

None of these patients had received any drug known to alter prolactin levels, in the preceding three months. Pregnant or lactating females were excluded, as were patients above 60 years of age. Patients with seizures symptomatic of febrile illnesses, metabolic imbalances, cerebrovascular accidents and degenerative or neoplastic disorders were not included.

The diagnosis of epilepsy was based on clinical features and an inter-ictal scalp EEG (wake and sleep record), using standard electrode placements. The classification of seizure type was based on the Revised International Classification of Epileptic Seizures (1981), with the exception that ictal and immediate post-ictal EEG recordings were not possible. In 10 of the 13 epileptic patients, the inter-ictal EEG was consistent with the seizure classification; the three patients with normal inter-ictal EEGs had well documented attacks and clearly demonstrated improvement in seizure control with treatment. Classification of seizure type was made prior to and blind to knowledge of serum prolactin levels. Only seizures occurring between 8 AM and 5 PM were studied.

In the patients receiving ECT, standard bifronto-temporal electrode placements and intermittent, pulsed current were used. Blood samples were collected between 8 AM and 10 AM after any one of the sessions that constituted the course of treatment.

Patients with pseudoepileptic seizures received a clinical diagnosis of hysterical conversion from the treating clinicians, and also fulfilled criteria for the diagnosis of pseudoseizures modified for the purpose of the study from those proposed by Desai et al. (1982), (see appendix). In 5 of the 11 patients, the interictal EEG was normal, in the remainder, the diagnosis of

hysterical conversion was so obvious that an EEG was clearly not indicated.

The 15 non-epileptic controls, matched for age (within 5 years), sex, were chosen from patients presenting with acute medical and surgical illnesses, to study the role of non-specific factors known to elevate prolactin levels, such as the stress of being ill, hospitalization, and the effects of various diagnostic or therapeutic procedures. The degree to which these patients were stressed was difficult to assess clinically, but attempts were made to select patients who were acutely and severely ill - e.g. patients with acute intestinal obstruction, traumatic paraplegia, compound fracture of long bones etc.

Samples of blood were taken from each patient at 5 minutes, 20 minutes and 1 hour after the observed seizure and a baseline sample 24 hours after the seizure, care being taken to ensure that the patient had been seizure free for at least 4 hours prior to the time of baseline sampling. In the patients undergoing ECT, a baseline sample was taken immediately prior to ECT. Samples from non-epileptic controls were taken serially after a diagnostic or therapeutic procedure. All samples were collected between 8 AM and 6 PM. In the majority of instances, samples were withdrawn via an indwelling catheter. The 216 samples collected were allowed to clot, centrifuged, serum separated and stored at -20°C till assay.

Prolactin estimations were done using a commercially available Kit (Biodata Products, Serono Diagnostics) that utilizes a double antibody method of radioimmunoassay. Prolactin assays were done blind to all clinical details. The estimations were done in two batches and all samples from an individual patient were analysed in the same batch. The sensitivity of this

method is 1.0 ng/ml. Normal values are < 25 ng/ml in females and < 15 ng/ml in males. In comparison with international standards, 1 ng Biodata prolactin = 23 mU WHO 75/504.

Results

The mean ages of the patients with epilepsy and hysterical pseudoseizures were $23.9 (\pm 8.5)$ and $21.0 (\pm 7.9)$, respectively. For patients undergoing ECT and for the controls the mean ages were $29.3 (\pm 9.0)$ and $26.6 (\pm 10.6)$ respectively. The mean age of the patients with hysterical pseudoseizures was significantly less than that of patients undergoing ECT ($P < 0.05$). No other significant differences were observed in the ages or sex of the patients in the various groups.

All patients with epilepsy had a post-ictal rise in serum prolactin values 5 minutes after the seizure, a peak at 20 minutes and values which were within normal limits by 1 hour (Fig. 1). Peak prolactin levels were greater than thrice baseline levels in all cases (3.7 - 17.9 fold increase: Table 1).

Table 1
Mean (\pm SD) and (Range) of serial prolactin values in the four groups

Sampling Time	Prolactin values (ng/ml)			
	Epileptics	Pseudoseizures	ECT	Controls
Baseline*	5.3 (\pm 1.9) (3.1-9.2)	4.9 (\pm 3.1) (5.9-14.7)	8.2 (\pm 5.0) (2.9-21.9)	11.7 (\pm 6.3) (3.9-26.5)
5 minutes	22.5 (\pm 9.4) (7.9-38.6)	15.4 (\pm 8.7) (2.8-27.7)	23.9 (\pm 14.5) (3.8-52.8)	15.4 (\pm 9.5) (4.1-33.8)
20 minutes	39.5 (\pm 12.8) (14.3-60.7)	13.2 (\pm 6.6) (3.0-22.1)	85.9 (\pm 41.3) (39.3-167.3)	13.6 (\pm 8.4) (5.4-34.9)
1 hour	12.5 (\pm 5.4) (6.8-23.9)	10.9 (\pm 4.5) (4.7-17.3)	37.1 (\pm 30.0) (8.7-138.8)	13.3 (\pm 9.4) (4.5-36.6)
Proportionate increase (20 min - baseline)	8.6 (\pm 4.6) (3.7-17.9)	1.4 (\pm 0.3) (1.0-1.8)	13.7 (\pm 9.5) (4.2-36.0)	1.3 (\pm 0.3) (0-1.7)

* = 5 minutes pre ECT level or 24 hours postictal/post event level
SD = Standard Deviation

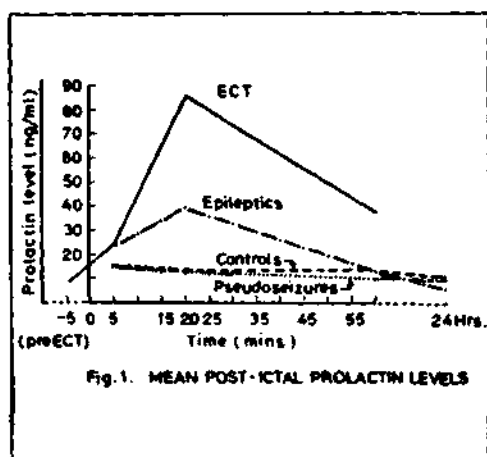


Figure 1

After hysterical pseudoseizures, the 20 minute prolactin value was within normal limits or only marginally elevated (Fig. 1); in no instance was there even a doubling of 20 minute levels over baseline values (Table 1). In 7 of the 11 patients, the prolactin peak occurred at 5 minutes.

After ECT, the pattern of rise was similar to that observed with epilepsy (Fig. 1). There was a greater than 4 fold increase at 20 minutes over baseline levels (Table 1), but the magnitude of the rise was greater than in patients with epilepsy (4.2 - 36.0 times baseline values).

The stressed, non-epileptic controls had prolactin values similar to that of the patients with pseudo-epileptic seizures, with the peak occurring at 5 minutes and a fall towards baseline by 20 minutes (Fig. 1). Prolactin values did not double over baseline values at 20 minutes and were lower than baseline levels in 3 cases.

Student's t-test was used to test the significance of mean prolactin changes at matched time periods between groups as well as for the magnitude of peak prolactin elevations (Table 2). The baseline levels of the epileptics were significantly lower than

Table 2
Comparison of prolactin levels at matched time periods between groups

Groups compared	Base-line	5 minutes	20 minutes	1 hour	Proportionate increase (20 minutes + 24 hours)
1 vs 2	4.574 (P<.001)	1.907 (NS)	6.168 (P<.001)	0.761 (NS)	4.674 (P+.001)
1 vs 3	1.971 (NS)	0.291 (NS)	3.889 (P<.001)	2.910 (P<.01)	1.763 (NS)
1 vs 4	3.532 (P<.01)	1.990 (NS)	6.435 (P<.001)	0.291 (NS)	5.526 (P<.001)
2 vs 3	1.060 (NS)	1.736 (NS)	5.763 (P<.001)	2.854 (P<.01)	3.867 (P<.001)
2 vs 4	0.828 (NS)	0.000 (NS)	0.114 (NS)	0.787 (NS)	1.165 (NS)
3 vs 4	1.697 (NS)	1.915 (NS)	6.657 (P<.001)	2.926 (P<.01)	4.535 (P<.001)

Group 1 = Epileptics

Group 2 = Pseudoseizures

Group 3 = ECT

Group 4 = Nonepileptic controls

* = Student's t test

that of the patients with pseudoseizures ($P < 0.001$) and the non-epileptic controls ($P < 0.01$), but not significantly lower than patients with endogenous depression undergoing ECT, an essentially non-epileptic group. The 20 minute post-ictal prolactin levels after epileptic seizures and ECT were significantly higher than that of the controls ($P < 0.001$) and following pseudoseizures ($P < 0.001$), as was the magnitude of increase over baseline levels ($P < 0.001$). At 1 hour, the mean prolactin levels after ECT were still elevated, but there were no significant differences between patients with pseudoseizures, controls and epileptics. There were no significant differences in prolactin levels between patients with pseudoseizures and stressed, non-epileptic controls at any of the time periods tested.

Since the epileptic group was not homogenous, the mean prolactin values of the two types of seizures were calculated

Table 3
Mean (+SD) and (Range) of serial prolactin values in epileptics and after ECT

Sampling Time	Prolactin values (ng/ml)		
	Complex partial seizures (n=8)	Tonic-clonic seizures (n=5)	ECT (n=15)
Baseline*	6.1(±2.1) (3.4-9.2)	4.0(±0.7) (3.1-4.9)	8.2(±5.0) (2.9-21.9)
5 minutes	22.4(±9.0) (7.9-32.0)	26.0(±10.4) (14.9-38.6)	23.9(±14.5) (3.8-52.8)
20 minutes	36.6(±14.0) (14.4-60.7)	44.3(±34.6) (34.6-58.3)	85.9(±41.3) (39.3-167.3)
1 hour	12.9(±6.3) (6.8-23.9)	11.8(±4.1) (6.9-18.1)	37.1(±30.0) (8.7-138.8)
Proportionate increase (20 mins + baseline)	6.9(±4.9) (3.7-17.9)	11.3(±2.8) (7.1-14.9)	13.7(±9.5) (4.2-36.0)

* = 24 hour postictal level or 5 minutes pre-ECT level.

SD = Standard Deviation

separately (Table 3). All 5 patients with generalized tonic-clonic seizures had peak prolactin values greater than 33 ng/ml (range 34.6 - 58.3 ng/ml; i.e. 795.8-1340 mU/ml). Of the 8 patients with complex partial seizures, 7 had peak prolactin levels greater than 25 ng/ml (25.4-60.7 ng/ml); i.e. 584.2-1396 mU/ml). One young male with complex partial seizures had a peak prolactin value of 14.4 ng/ml, which was just within normal limits. After generalized seizures, there was a greater than 7 fold increase in peak prolactin values over baseline levels (7.1 - 14.9 fold rise). After complex partial seizures, peak increase were greater than thrice baseline prolactin values (3.7 - 17.9 fold rise). Even the patient with peak prolactin levels within normal limits had a 3.7 fold rise over baseline concentration.

Although peak prolactin values were

greater following ECT than those seen in the epileptics as a group ($P < 0.001$), the differences were less significant when the epileptic group was homogenized into complex partial and generalized tonic-clonic seizures ($P < 0.01$ and < 0.05 , respectively; Table 4).

Correlation coefficients were calculated for possible correlations between age and sex of patients, duration of seizures and peak prolactin values. No significant correlation between any of these variables and peak prolactin values was evident.

Table 4
Comparison of prolactin levels between epileptics & ECT patients

Sampling time	t values* of groups compared†		
	1 vs 2	1 vs 3	2 vs 3
1. Baseline	2.079	1.440	1.820
2. 5 minutes	0.633	1.055	0.302
3. 20 minutes	1.080	3.257 ($P < .01$)	2.197 ($P < .05$)
4. 1 hour	0.320	2.234 ($P < .05$)	1.842
5. Proportionate increase**	1.792	1.874	0.557

† Group 1: Complex partial seizures; 2: Generalized tonic clonic seizures; 3: ECT

* Student's t test

** 20 minutes + 24 hours

Discussion

The results of this study provide clear evidence of significant post-ictal hyperprolactinemia following clinically observed complex partial seizures, generalized tonic-clonic seizures and generalized convulsions induced by ECT. Prolactin changes after hysterical pseudoseizures were negligible and similar to those observed in stressed, non-epileptic controls, with elevations, if any, occurring in the 5 minute sample and possibly reflecting the influence of non-specific stress factors.

The baseline values of the epileptics were within normal limits, as was also observed by Pritchard et al. (1983). The apparently maximally stressed non-epileptic controls had the highest baselines values, suggesting a possible casual role for stress in the base line differences in prolactin levels observed among the various groups.

Apart from stress, strenuous muscular activity is also known to rise prolactin levels. However, in this study complex partial seizures without convulsive components were associated with significant hyperprolactinemia, while pseudo-epileptic seizures with significantly greater overall muscular activity were not, thus pointing to specific neuronal mechanisms as the cause for the hyperprolactinemia. The most plausible explanation seems to be that the abnormal seizure activity on spreading to the hypothalamus from medial temporal structures disrupts the tonic inhibition by the tuberoinfundibular dopaminergic neurons on anterior pituitary prolactin release (Dana-Haeri et al. 1983). The role of other neurotransmitters and endogenous opioid peptides, if any, in the postictal hyperprolactinemia, remains unclear.

In the study by Laxer et al. (1985), there was a positive relationship between the complexity of automatisms in complex partial seizures and peak prolactin levels. There was a suggestion that this relationship held true for the patients with complex partial seizures in the present study. The patient with the briefest complex partial seizure and simplest automatisms also had the lowest postictal prolactin concentration, while a patient with ambulatory automatisms and posturing had the highest peak postictal elevation.

Applying the cut off levels proposed by Trimble and co-workers (Trimble

1978; Dana-Haeri et al. 1983), to the patients in this study, produced no false positives among the patients with pseudo-seizures. However, 2 of the 5 patients with generalized tonic clonic seizures and 1 of the 8 patients with complex partial seizures were wrongly classified; a false negative rate of 40% and 12.5% respectively.

Redefining significant hyperprolactinemia as a three fold increase in the peak prolactin levels over baseline values increased the sensitivity of the test to 100% while leaving the specificity unaltered. Similar results were obtained when the re-defined cut off value based on proportionate increases in prolactin values was applied to the postictal values of the 56 patients in Laxer's (1985) study. In the study by Pritchard et al. (1985) two of the five patients with complex partial seizures had only a 2.5 fold increase in prolactin levels, while the other three had greater than three fold increases. However, since only 15 minute and 30 minute samples were used, it is possible that a prolactin peak at 20 minutes in these two patients was missed.

It is therefore proposed, that in cases of complex partial seizures with behavioural automatisms and generalized tonic-clonic seizures, the prolactin value 20 minutes after the event, would show a greater than 3 fold increase over a baseline done 24 hours after the event, and would help differentiate such cases from patients with pseudoepileptic seizures. Prerequisites for the application of this test would be a normal baseline prolactin level and a 3-4 hour seizure free period prior to testing for baseline levels. Rises in prolactin levels of this magnitude may not be observed after generalized tonic-clonic seizures of less than 30 seconds duration, after complex partial seizures without automatisms and exhibiting only behavioural arrests or

auras, and perhaps in young children and the elderly. On the other hand, it can be confidently expected that even after pseudo-epileptic seizures involving a significant amount of motor activity, serum prolactin levels would not show a three fold increase over baseline levels at 20 minutes.

Another clinical situation where postictal hyperprolactinemia may prove useful is in the detection of pseudoepileptic seizures in epileptic patients. Our experience with a patient where such a differentiation was possible, will be reported separately.

The general findings of this study are similar to those reported in other studies with similar sample sizes (Pritchard et al. 1985; Collins et al. 1983; Bye et al. 1985). The study is being continued to increase the sample size, however, our preliminary conclusions are that transient postictal hyperprolactinemia is a sensitive biochemical marker of a epileptic seizure and of potential use as an adjunct in the differentiation of epileptic from hysterical pseudoepileptic seizures.

Acknowledgement

This work was supported by a grant from the Fluid Research Fund of the Christian Medical College. The authors gratefully acknowledge the assistance of Dr. A.S. Kanagasabapathy and Mrs. Geetha Krishnan, Department of Clinical Biochemistry, with prolactin assays, and Dr. J. Richard, Department of Biostatistics, with the statistical analysis.

References

- ABBOTT, R.J., BROWNING, M.C.K. & DAVIDSON, D.L.W. (1980). Serum Prolactin and Cortisol concentrations after grandmal seizures' *Journal of Neurology, Neurosurgery and Psychiatry*, 43, 164-167.
- BYE, A.M.E., NUNN, P.K. & WILSON, J. (1985). Prolactin and seizure activity. *Archives of Disease in Childhood*, 60, 848-851.
- COLLINS, W.C.J., LANIGAN, D. & CALLAGHAN, N. (1983). Plasma prolactin concentrations following epileptic and pseudoepileptic seizures. *Journal of Neurology, Neurosurgery and Psychiatry*, 46, 505-508.
- COMMISSION FOR CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY, (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, 22: 489-502.
- DANA-HAERI, J., TRIMBLE, M.R. & OXLEY, J. (1983). Prolactin and gonadotrophin changes following generalized and partial seizures. *Journal of Neurology, Neurosurgery and Psychiatry*, 46, 331-335.
- DEAKIN, J.F.W., FERRIER, I.N., CROW, T.J., JOHNSTONE, E.F. & LAWLER, P. (1983). Effects of ECT on Pituitary Hormone Release: Relationship to seizure, clinical variables and outcome. *British Journal of Psychiatry*, 143, 618-624.
- DESAI, B.T., PORTER, R.J., & PENRY, K. (1982). Psychogenic seizures. A study of 42 attacks in six patients with intensive monitoring. *Archives of Neurology*, 39, 202-209.
- FENTON, G.W. (1986). Epilepsy and Hysteria. *British Journal of Psychiatry*, 149, 28-37.
- LAXER, K.D., MULLOOLY, J.P., & HOWELL, B. (1985). Prolactin changes after seizures classified by EEG monitoring. *Neurology*, 35, 31-35.
- OHMAN, R., WALINDER, J., BALLDIN, J. & WALLIN, L. (1976). Prolactin response to electroconvulsive therapy. *Lancet*, ii, 931-937.
- PRITCHARD, P.B., WANNAMAKER, B.B., SAGEL, J., NAIR, R. & DeVILLIER, C. (1983). Endocrine function following complex partial seizures. *Annals of Neurology*, 14, 27-32.
- PRITCHARD, P.B., WANNAMAKER, B.B., SAGEL, J. & DANIEL, M. (1985). Serum Prolactin and Cortisol levels in the evaluation of pseudoepileptic seizures. *Annals of Neurology*, 18, 87-89.
- TRIMBLE, M.R. (1978). Serum prolactin in epilepsy and hysteria. *British Medical Journal*, ii, 1682.
- TRIMBLE, M.R. (1986). Pseudoepileptic seizures. *Neurologic Clinics*, 4, 531-548.
- WYLLIE, E. LUDERS, H., MACMILLAN, J.P. & GUPTA, M. (1984). Serum Prolactin levels after Epileptic Seizures. *Neurology*, 34, 1601-1604.

APPENDIX

Criteria for the diagnosis of hysterical pseudoepileptic seizures (Modified from Desai et al. 1982).

I. Major Criteria

All patients must satisfy all three of the following:

- a) The seizure does not conform to known seizure types as described in the Revised International Classification of Epileptic Seizures, 1981.
- b) The interictal EEG, if indicated, is normal.
- c) If on anticonvulsant medication, the frequency of attacks is not influenced by changes in medication regimen.

II. Secondary Criteria

Five of the following seven criteria must be fulfilled:

- a) Gradual, non-paroxysmal onset without clear cut aura or warning of impending attack.
- b) Avoidance or escape from conflicting situations seem to underly seizures, and/or benefits from relatives in the form of attention, material gain, or escape from responsibilities seem to perpetuate seizures.
- c) Absence of postictal confusion, lethargy or drowsiness.
- d) Absence of postictal subjective complaints.
- e) Attacks frequently induced by suggestion.
- f) Postictal recollection of events during attacks.
- g) Violent behaviour during attacks, if present, is highly directed.

III. Minor Criteria

Six of the nine minor Criteria must be fulfilled:

- a) Attacks do not occur during sleep.
- b) Tongue biting does not occur during seizures.
- c) Other injuries are not sustained during attacks.
- d) Urinary incontinence does not occur during attacks.
- e) Attacks do not follow a consistent pattern.
- f) Attacks invariably occur in the presence of an audience.
- g) Neurological examination immediately after an attack is normal.
- h) Hysterical character traits are present in the premorbid personality.
- i) Past history of episodes suggestive of hysterical conversion or dissociation.