Diagnostic value of serum prolactin levels in PNES in the epilepsy monitoring unit

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Abstract

Background: This is a retrospective study to determine the usefulness of serum prolactin levels in the epilepsy monitoring unit (EMU) for distinguishing psychogenic nonepileptic seizures (PNES) from epileptic seizures (ES). **Methods:** All the records of consecutive patients admitted to the EMU between 2008 and 2012 were reviewed. Patients with a diagnosis of PNES and ES were selected. Serum prolactin level was obtained within 20 minutes for all patients, and an elevated prolactin level was defined as twice the patient's baseline value. A total of 607 records were reviewed, and 389 patients were excluded because

of incomplete information or lack of a clinical event. **Results:** A total of 218 patients were included in the analysis. A further 18 patients were excluded because of simple partial seizures or because the documented time of obtaining serum prolactin was not clear. A total of 146 patients had PNES, of which 42 had elevated prolactin levels, representing a 28.8% false-positive rate. All 22 patients with generalized tonic-clonic seizures had elevated serum prolactin; however, 5 of 32 patients with complex partial seizures did not have an elevated prolactin level, representing a 15.6% false-negative rate. **Conclusions:** Serum prolactin levels do not provide any additional support for distinguishing PNES from ES. Furthermore, serum prolactin levels in this setting add unnecessary blood draws and financial burden for the patients. Therefore, prolactin levels should not be obtained routinely in the EMU. **Classification of evidence:** This study provides Class III evidence that postevent elevation of serum prolactin occurs in 84.4% of patients with ES and 28.8% of patients with PNES. *Neurol Clin Pract* 2016;6:116-119

Psychogenic nonepileptic seizures (PNES) account for 10%–40% of patients referred to epilepsy centers.^{1,2} Clinicians are often faced with the challenging task of distinguishing between PNES and epileptic seizures (ES). Clinical features of ictal events correctly differentiate PNES from ES in less than 70% of cases.^{3,4} Even when a patient's typical events are recorded during video-EEG, artifacts often obscure scalp EEG during violent motor movements. Serum prolactin, a pituitary hormone that is elevated during generalized ES, has been reported to differentiate epileptic from hysterical seizures.⁵ However, subsequent

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Editorial, page 100

Misdiagnosis of psychogenic nonepileptic seizures has substantial morbidity, social effect, and economic burden on the health care system.

studies demonstrated that serum prolactin was elevated in temporal lobe epilepsy but not frontal lobe epilepsy, which may lead to erroneous diagnosis of the latter as PNES.⁶

The American Academy of Neurology (AAN) guidelines on the use of serum prolactin in diagnosing ES stated that elevated serum prolactin 10–20 minutes after a clinical event is probably useful in differentiating ES from PNES (Level B).⁷ Misdiagnosis of PNES has substantial morbidity, social effect, and economic burden on the health care system.

In this study, we set out to retrospectively assess the serum prolactin level in a series of patients with the diagnosis of PNES who were admitted to the epilepsy monitoring unit (EMU). We expected that serum prolactin would not rise following a clinical event in PNES.

METHODS

This is a retrospective chart review of consecutive patients admitted to the EMU between 2008 and 2012. All the patients underwent continuous video-EEG recording using the International 10-20 System of electrode placement to establish the diagnosis. The duration of video-EEG recording averaged 3.6 days. The diagnosis of PNES was established using video-EEG and placebo challenge. The placebo challenge had to produce the same constellation of symptoms associated with the patient's typical event for the diagnosis of PNES.⁸

All the patients had serum prolactin drawn on the day of admission as the baseline and within 20 minutes following a clinical event. An elevated serum prolactin level following a clinical event was defined as a level at least twice the baseline level. Each individual is represented only once across all data points, and there was no inclusion of multiple events per patient. We compared the patients with PNES to consecutive patients with ES.

We report the sensitivity and specificity of serum prolactin level in patients with PNES and ES. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) can be derived from the following formulas: sensitivity = $TP/TP + FN$, specificity = $TN/TN + FP$, PPV = $TP/TP + FP$, and NPV = $TN/TN + FN$. Where, TP = total positive, FN = false-negative, TN = total negative, and FP = false-positive.

Standard protocol approvals, registrations, and patient consents

The study received approval from an ethical standards committee on human experimentation (University of Mississippi) for any experiments using human subjects.

RESULTS

A total of 607 records were reviewed, and 389 patients were excluded because of incomplete information or lack of a clinical event. Therefore, 218 patients were included in the analysis. A further 18 patients were excluded (5 patients with simple partial seizures [SPS] and 13 patients for whom there was no clear documentation of the time when the blood was drawn for prolactin level). We felt that those patients with SPS may not have had enough symptoms to raise serum prolactin levels. Thus 146 patients (66.5% women) were diagnosed with PNES (mean age 27.7 years; range 20–68). Forty-two of 146 patients with PNES had elevated serum prolactin levels, representing an FP rate of 28.8%. Fifty-four of 200 consecutive patients were diagnosed with ES (mean age 36.7 years; range 21–71) and 51.9% were females. Twenty-two patients had generalized tonic-clonic seizures (GTC) and 32 had complex partial seizures (CPS) only. All of the 22 patients with GTC had elevated serum prolactin; however, 5 of 32 patients with CPS did not have elevated serum prolactin, representing a 15.6% FN rate.

Table Confusion matrix of the actual serum prolactin elevation levels as a function of ES vs PNES

Prolactin levels	GTC/CPS	PNES
Elevated	84.4%	28.8% (false-positive)
Not elevated	15.6% (false-negative)	72.2%

Abbreviations: CPS = complex partial seizures; ES = epileptic seizures; GTC = generalized tonic-clonic seizures; PNES = psychogenic nonepileptic seizures.

Sensitivity and specificity scores are presented in the table for the detection of GTC (sensitivity 100%, 95% confidence interval [CI] 85.1%–100%), CPS (sensitivity 84.4%, 95% CI 68.2%–93.1%), and PNES (specificity 71.2%, 95% CI 63.4%–78%). Overall, serum prolactin had a specificity of 56.2% and a PPV of 53.8%.

DISCUSSION

This study demonstrates that serum prolactin has no added diagnostic value in the EMU. Furthermore, it may confuse the clinical diagnosis by adding FP and FN results. In addition, the measurement of serum prolactin adds unnecessary drawing of blood and a financial burden to the patient. Therefore, we recommend that serum prolactin levels should not be obtained routinely in the EMU.

A prospective study⁹ compared 38 patients with ES to 20 patients with pseudoseizures. The absolute rise in serum prolactin level following a clinical event was evaluated, and it was found that there is significant overlap in the rise of serum prolactin between patients with pseudoseizure and patients with ES. However, only a small number of patients were included, and postevent prolactin levels were obtained 2 hours after the clinical event, which may have affected the absolute level of serum prolactin. Another study¹⁰ reported that 1 of 21 patients with PNES had a significant elevation of serum prolactin, which is similar to an earlier report¹¹ showing that 2 of 14 patients (14.3%) with PNES had elevation of serum prolactin of twice the baseline measurement. When we evaluated a larger number of patients, the percentage of FP serum prolactin elevation in individuals with PNES rose to 28.8% (42 of 146), indicating that serum prolactin elevation measures are not good at differentiating between PNES and ES. Hence, research findings are in general agreement that the observed rise in serum prolactin levels could be falsely attributed to epileptic activity in 14%–29% of patients.

The AAN report stated that measuring the serum prolactin assay in an appropriate clinical setting 10–20 minutes after a suspected clinical event is useful to differentiate GTC or CPS from PNES among adults (Level B evidence).⁷ The AAN recommendation of the 10–20-minute time interval was based on a series of small studies and there was no mention of any cost regarding the use of serum prolactin levels. Despite the small number of patients, these studies commonly reported several cases of PNES with elevated serum prolactin postevent. Together with our evidence, it is clear that the statement regarding the use of serum prolactin levels as Level B evidence is premature. Our findings clearly demonstrate that the serum prolactin levels are elevated in a large number of patients with PNES, resulting in an erroneous diagnosis of these patients. Thus postevent serum prolactin has limited reliability in the differentiation between epileptic and nonepileptic events in a clinical setting.

In addition, we discovered that the cost of assaying serum prolactin in our institution is \$220 US per patient. This results in a total cost of \$248,820 US for the study period (1,131 total prolactin levels were drawn). Certainly this created a financial burden to the health care system and wasted financial resources that could well be directed toward better management of these patients. Therefore, we advocate that regular use of serum prolactin levels may not be cost- and

This study demonstrates that serum prolactin has no added diagnostic value in the epilepsy monitoring unit.

time-effective and that alternative diagnostic measures may be of greater value in the diagnosis of patients with pseudoseizures.

A limitation of our study is that it is retrospective and was carried out at a tertiary level 4 epilepsy center, which may result in some selection bias. However, this large study supports the conclusion that postevent serum prolactin has limited value in the clinical diagnosis of ES vs PNES.

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