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ORIGINAL COMMUNICATION

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Does serum prolactin indicate the presence of seizure in the emergency department patient?

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Abstract *Study objective* We sought to evaluate whether there was a correlation between elevated serum prolactin in patients presenting with the question of seizure. *Methods* A Convenience sample of 200 consecutive patients were chosen who had a serum prolactin measurement in the setting of seizure activity. *Results* The prolactin level was within a range of 3.90–294.00 mg/dl with an upper limit of normal being 29.9 mg/dl. Patients were ultimately diagnosed with seizure in 54.5 % (109 of 200) with an abnormal prolactine in 31.0 % (62 of 200). The sensitivity of this serum prolactin was 42 %, the specificity was 82 %, positive predictive value (PPV) of 74 %, and negative predictive value (NPV) of 54 %. There was an overall accuracy of 60 % in the diagnosis of seizure, with a likelihood ratio of 2.4 (95 % Confidence Interval [CI], 1.5–3.9). *Conclusion* The measurement of serum prolactin is helpful as a confirmatory test, but not as screening test in the emergency department setting.

Key words serum prolactin · seizure · emergency

Introduction

A seizure is described as altered neurological function associated with abnormal cerebral electrical activity manifested as a movement, sensory or cognitive disorder. Although this appears to be a straightforward description, it sometimes is in contrast to the difficult dilemma of proper diagnosis of seizure in the emergency department (ED). New onset seizure can be associated with infection, metabolic derangements, trauma, drug intoxication or withdrawal but most commonly is cryptogenic in origin.

A common dilemma encountered in the ED is to distinguish between seizure, syncope or pseudoseizure (a functional event not associated with abnormal cerebral electrical activity). The diagnostic armamentarium implemented in the acute setting is often poorly discriminatory with few diagnoses made secondary to hypoglycemia, hyponatremia or leukocytosis, although routine laboratory testing is often ordered.

Interestingly serum prolactin (PRL), an anterior pituitary lactogenic hormone has been reported to be associated with an acute seizure. The hormone release is caused by the propagation of epileptic activity from temporal lobe to the hypothalamic-pituitary axis in 60 % of complex partial seizures, and is associated with a 2- to 3 fold increase in those with posttraumatic seizures [1, 2]. There has not been a rigorous evaluation of this association between an elevated prolactin, and the presence of seizure in the emergency medicine population to date.

We hypothesized an association between seizure activity and an elevated prolactin, helping to facilitate diagnosis of this condition in the emergency department.

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Materials and methods

This retrospective non-randomized study that enrolled 200 consecutive patients in a convenience sample in which serum prolactin level was estimated in patients who presented to the emergency department with a clinical symptom complex consistent with seizure, manifested as near or total loss of consciousness, over a one year period accompanied by abnormal motor activity and/or a post-ictal phase. (Fig. 1) Their laboratory data, in particular serum prolactin levels were then accessed directly. Exclusion criteria included trauma patients and children aged under 18 years. Serum prolactin level was determined as part of the routine seizure protocol in the acute setting, which also included glucose and sodium levels using a commercial sandwich immunoassay method with a normal level of 2.8–29.9 mg/ml (ADVIA Centaur® System, Bayer Co.) (Fig. 1).

The primary endpoint was a hospital discharge diagnosis of seizure either initially or at the end of the stay. The diagnosis was recorded from ED records if discharged or inpatient discharge record if admitted. The presence of an abnormal electroencephalogram indicated by abrupt onset and termination of repetitive rhythmic activity usually consisting of a sharp or spike wave pattern, during the hospital stay if performed was included as well. Nonspecific EEG activity consisting of diffuse slowing or other nonspecific patterns were not considered diagnostic for seizure.

Information was abstracted after the study, from the patient medical records, particularly EEG reports and hospital discharge diagnoses. This study was approved by the UPMC Northwest Institutional Review Board. Data were represented as mean, range and chi square analysis was used for intergroup comparisons.

Results

Two hundred patients were enrolled with the diagnosis of seizure in 132 (66 %) followed by syncope 36 (18 %), as well as other miscellaneous causes such as transient ischemic attack, pneumonia, or metabolic derangements, with four excluded because of medical record omissions (Table 1). The prolactin level was within a range of 3.90–294.00 mg/dl with an upper limit of normal being 29.9 mg/dl. An elevated prolactin was found in the presence of seizure in 42 % (46 of 109) of patients compared with 17.5 % (16 of 91) without seizure. The sensitivity for prolactin in the diagnosis of seizure was 42 % with a specificity of 82 %. This was accompanied by a positive predictive value (PPV) of 74 %, a negative predictive value (NPV) of 54 %, and an overall accuracy of 60 % (Table 2).

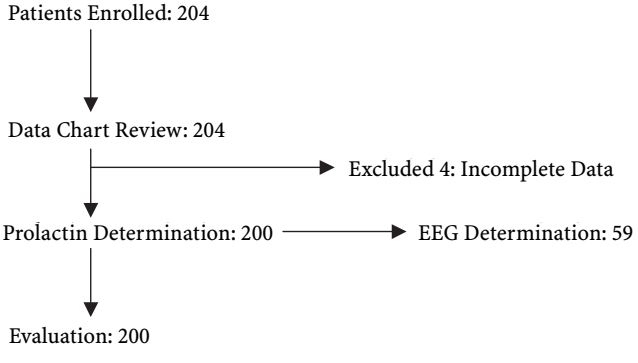

Fig. 1 Trial Profile

Table 1 Patient Diagnosis

Patients Enrolled (N = 200)	N	%
Seizure	132	66
Syncope	36	18
Transient Ischemic Attack	4	2
Pneumonia	4	2
Metabolic Hypoglycemia Hyponatremia	4	2
Drug/Alcohol Toxicity	4	2
Miscellaneous Migraine Abdominal Pain SAH Viral Syndrome	16	8
	200	100 %

The second correlation analysis evaluated the association between abnormal prolactin and EEG. There were only 26 EEGs performed in the 24 % of patients who showed chronicity of the complaint. There was a significant correlation between abnormal prolactin level and the diagnosis of seizure (P = 0.0002), but not the presence of an abnormal EEG (P = 0.4708) performed at some point in the hospital course (Table 3). The likelihood ratio was 2.4 (95 % CI, 1.5–3.9) for the

Table 2 Prolactin and Presence of Seizure Association

Prolactin	Seizure:	Absent	Present	
Normal		75 (54.3) (82.4)	63 (45.6) (57.8)	138 (69)
Abnormal		16 (25.8) (17.6)	46 (74.1) (42.2)	62 (31)
		91 (45.5)	109 (54.5)	200 (%)
Chi-Square p = 0.000178)				
		Value	95 % C. I.	
Prevalence/Pretest Probability		0.5450	0.4760–0.6140	
Sensitivity		0.4220	0.3293–0.5147	
Specificity		0.8242	0.7460–0.9024	
Diagnostic Accuracy		0.6050	0.5372–0.6728	
Positive Predictive Value		0.7419	0.6330–0.8509	
Posttest Probability Test+		0.7419	0.6330–0.8509	
Likelihood Ratio Test+		2.4002	1.4614–3.9421	
Negative Predictive Value		0.5435	0.4604–0.6266	
Posttest Probability Test–		0.4565	0.3734–0.5396	
Likelihood Ratio Test–		0.7013	0.5820–0.8450	

Table 3 Prolactin and Encephalogram Association

	Prolactin		
	Normal	Abnormal	
Normal	27 (67.5) (71.0)	13 (32.5) (61.9)	40 (67.8)
EEG			
Abnormal	11 (57.9) (29.0)	8 (42.1) (38.1)	19 (32.2)
	38 (64.4)	21 (35.6)	59 (%)
Chi-Square p = 0.470842			
	Value	95% C. I.	
Prevalence/Pretest Probability	0.3559	0.2338–0.4781	
Sensitivity	0.3810	0.1732–0.5887	
Specificity	0.7105	0.5663–0.8547	
Diagnostic Accuracy	0.5932	0.4679–0.7186	
Positive Predictive Value	0.4211	0.1990–0.6431	
Posttest Probability Test+	0.4211	0.1990–0.6431	
Likelihood Ratio Test+	1.3160	0.6288–2.7542	
Negative Predictive Value	0.6750	0.5298–0.8202	
Posttest Probability Test–	0.3250	0.1798–0.4702	
Likelihood Ratio Test–	0.8713	0.5886–1.2896	

presence of seizure in the setting of an elevated prolactin.

Discussion

Previous work has evaluated the utility of prolactin in identifying children with seizures. Fein in a study of 35 children noted a PPV of 65% and NPV of 76% in the diagnosis of tonic-clonic seizures [3]. Likewise, hyperprolactinemia has been reported to follow febrile seizures, as well as noting an 83% increase from baseline of 202 to 370 mU/l in this clinical setting [4]. Interestingly, there seems to be a tachyphylaxis-like response with depletion of the releasable protein. Response was clearly more robust after a shorter seizure-free interval (1 to 25 hours) rather than a longer (31–240 hours) period [5]. However, with status epilepticus the PRL rise continued after each seizure (2 to 6 episodes) in 3% of patients [6].

There have been several evaluations attempting to utilize serum PRL to assist in seizure diagnosis. The most common competing differential diagnosic dilemma involves syncope characterized by a loss of consciousness and falling; and distinction is based on a lack of postictal period, although incontinence can occur in both [7]. However, as a distinguishing feature hyperprolactinemia can be seen in either seizure or syncope. Oribe performed a tilt table analysis with 11 of 21 patients demonstrating a four fold rise in PRL (9–52 ng/ml), while it remained unchanged in those without tilt induced syncope [8].

In the emergency department setting Cordingly found an increase in PRL in 8 of 11 syncope cases with follow up levels returning to normal in the post-ictal phase [9]. This study also failed to distinguish those patients with seizure from syncope.

Lastly PRL has been utilized to help distinguish seizure from pseudoseizure. Alving evaluated 38 patients with simple or complex partial seizures with or without secondary generalization corroborated by EEG monitoring [10]. He found only a sensitivity of 20% and a NPV of 40% differentiating seizure from pseudoseizure.

Our study found that the use of PRL to assist in seizure diagnosis was helpful with goal directed endpoints. Its use as a screening test was only modestly effective with poor sensitivity (42%), but excellent positive predictive value (74%). Its use as a confirmatory test, however, was better with a specificity of 82% and negative predictive value of 54%. However, the overall accuracy was only 60%, but was associated with a 2.4 fold likelihood of disease. In and of itself, this does not necessarily establish diagnostic utility in clinical practice requiring a likelihood increase of 8–10 fold to be clinically relevant.

There seemed to be internal inconsistency due to incorporation bias with the test used to make the diagnosis. This occurs since there is no gold standard test for seizure, as the EEG is often performed at some later point in the course of the illness. Therefore the PRL value may have been incorporated into the diagnosis linking the test and result inappropriately. This factor was greater for diagnosis in the emergency department than for the subsequent inpatient discharge diagnosis.

We attempted to minimize the effect by utilizing the discharge diagnosis for the hospital stay. A further study will be begun to measure PRL in a blinded fashion to better elucidate this relationship. The study was not designed to differentiate between seizure and syncope, nor to utilize EEG as the diagnostic endpoint. Since only 25% of patients received this test it is not used enough to be meaningful, so clinical diagnosis remained the endpoint. But this laboratory test was helpful to "diagnose" seizure if the PRL was elevated, as well as noting a normal PRL when seizure was not present.

Conclusion

The use of serum prolactin is a reliable confirmatory test, but is only modestly effective as a screening test for seizure or syncope. However, in light of its low cost compared with EEG as well as ready availability in the emergency department, it retains some usefulness.

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