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Use of serum prolactin in diagnosing epileptic seizures

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

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Abstract—Objective: The purpose of this article is to review the use of serum prolactin assay in epileptic seizure diagnosis. **Methods:** The authors identified relevant studies in multiple databases and reference lists. Studies that met inclusion criteria were summarized and rated for quality of evidence, and the results were analyzed and pooled where appropriate. **Results:** Most studies used a serum prolactin of at least twice baseline value as abnormal. For the differentiation of epileptic seizures from psychogenic nonepileptic seizures, one Class I and seven Class II studies showed that elevated serum prolactin was highly predictive of either generalized tonic-clonic or complex partial seizures. Pooled sensitivity was higher for generalized tonic-clonic seizures (60.0%) than for complex partial seizures (46.1%), while the pooled specificity was similar for both (approximately 96%). Data were insufficient to establish validity for simple partial seizures. Two Class II studies were consistent in showing prolactin elevation after tilt-test-induced syncope. Inconclusive data exist regarding the value of serum prolactin following status epilepticus, repetitive seizures, and neonatal seizures. **Recommendations:** Elevated serum prolactin assay, when measured in the appropriate clinical setting at 10 to 20 minutes after a suspected event, is a useful adjunct for the differentiation of generalized tonic-clonic or complex partial seizure from psychogenic nonepileptic seizure among adults and older children (Level B). Serum prolactin assay does not distinguish epileptic seizures from syncope (Level B). The use of serum PRL assay has not been established in the evaluation of status epilepticus, repetitive seizures, and neonatal seizures (Level U).

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Prolactin (PRL) release from the pituitary is controlled by the hypothalamus via a PRL inhibitory factor, now believed to be dopamine.¹ It has been hypothesized that ictal epileptic activity in the mesial temporal structures may propagate to the hypothalamus, altering the hypothalamic regulation of PRL release.²

Trimble first demonstrated that generalized tonic-clonic seizures, but not nonepileptic seizures (NESs), could raise serum PRL.³ Despite subsequent confirmatory findings, the sensitivity and specificity of serum PRL assay for diagnosis of epileptic seizures (ESs) remain uncertain. Utility of PRL assays for diagnosis of seizures depends upon the study design, standard of seizure classification, and criteria for abnormal PRL elevation. Additional uncertainty arises from the circadian fluctuations of serum PRL, dem-

onstrating surges of 50 to 100% prior to awakening from sleep, although PRL serum levels otherwise are stable during the waking state.⁴ PRL concentrations usually are higher in females than in males,⁵ and higher in persons with epilepsy than in healthy individuals.⁶ In a study that measured baseline PRL every 20 minutes over 24 hours in 20 healthy controls and 17 people with epilepsy,⁵ no female had baseline PRL exceeding 700 μ U/mL, and no male exceeded 450 μ U/mL. However, the study subjects endured disrupted sleep, and thus the effect from nocturnal PRL rises could not be fully established. Psychogenic or physiologic nonepileptic events also can influence serum PRL level. Several studies^{7–10} have suggested that serum PRL can increase after syncope, a common imitator of epilepsy.

Recent interest in the use of PRL has diminished

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with the availability of video-EEG monitoring. However, a serum marker continues to be of potential clinical utility, especially when video-EEG is not readily available. Based on the evidence classification scheme of the American Academy of Neurology (AAN), we propose recommendations for the use of serum PRL assay to differentiate ES from psychogenic NES. We also reviewed the usefulness of serum PRL in other settings, such as following syncope and repetitive seizures and in the neonatal population.

Methods. We searched MEDLINE, Science Citation Index, and the Cochrane Database, combining the search term *prolactin* with the terms *seizure(s)*, *pseudoseizure(s)*, *epilepsy*, *syncope*, or *status epilepticus*. Three hundred ninety-six articles were identified as of March 2005. We reviewed the abstracts of these articles, specifically looking for controlled studies that reported on PRL changes following seizures or seizurelike events. Reviews without original data, letters, meeting abstracts, and case reports/series were excluded.

We examined 41 articles in their entirety, along with 5 additional articles identified upon reviewing bibliographies of the retrieved articles. Three articles in German were translated into English. We categorized the articles into two groups: Group 1 consisted of controlled studies investigating the use of postevent PRL to discriminate ES from psychogenic NES. Group 2 consisted of controlled studies assessing serum PRL changes following syncope, repetitive seizures, or neonatal seizures. For Group 1, we selected studies for inclusion into our analysis based on the following criteria: 1) prospective design, 2) implementation of reference standard in the form of continuous EEG monitoring, 3) specification of the threshold for PRL elevation and the postevent lapse time of PRL measure, 4) reporting of the accuracy rates of PRL assay among case and control groups, and 5) publication in a peer-reviewed journal. For Group 2, all published studies that prospectively investigated serum PRL changes following tilt-induced and monitored syncope, repetitive seizures, status epilepticus (SE), or neonatal seizures were included. Wherever a study reported more than one criterion for elevated PRL, we analyzed the data arising from criterion closest to the common criteria chosen by other studies of the same group (i.e., twice baseline level, or >36 ng/mL for Group 1). PRL measures presented in μ U/mL or μ g/L were converted for consistency of presentation to ng/mL. We graded each study using the four-tiered classification-of-evidence scheme in Appendix 1.

Most laboratories report PRL upper normal limits of 18 to 23 ng/mL.^{11,18} However, prior literature does not specify a precise and commonly accepted cutoff PRL level as an indicator of epilepsy.¹² We accepted the individual investigators' opinion of abnormal PRL elevation. From the proportion of elevated PRL for each seizure type reported, we calculated sensitivity and specificity, where appropriate. Ninety-five percent CIs for each parameter were calculated using the Wilson score method without continuity correction.¹³ From all Class I and Class II studies, the sensitivity values were then pooled by calculating the weighted average. The same process was performed for the specificity values. Applying Bayes' theorem, the positive or negative predictive values of serum PRL assay would depend not only on the sensitivity and specificity parameters, but also on the pretest probability that an event is epileptic.¹¹ We calculated the predictive values for a range of ES pretest probabilities from 99% to 50%, assuming the respective pooled sensitivity and specificity for generalized tonic-clonic seizures (GTCs), complex partial seizures (CPSs), and all ESs combined.

We set the requirement that both patient sample size and number of seizures studied must be 50 or greater for a study to be considered "wide spectrum" for the purpose of evidence classification. The varieties of seizure types studied were also weighed in assessing extent of patient spectrum.

Analysis of evidence. *Question 1: Is serum PRL assay useful in differentiating ES from psychogenic*

NES? One Class I and nine Class II studies compared serum PRL changes following ES and psychogenic NES (table 1).¹⁴⁻²³ Of these 10 studies, all except one study¹⁵ ascribed psychogenic etiologies to the NES. The terminology of NES was used in one study that did not elaborate on etiology.¹⁵ In one Class I and seven Class II studies, elevated serum PRL measures were positively predictive of a correct diagnosis of GTC or CPS, whereas failure of PRL elevation poorly distinguished between ES and psychogenic NES. Data were insufficient to establish the predictive value of PRL following simple partial seizures. Two Class II studies^{14,16} showed a small but significant PRL elevation following psychogenic NES and reported the lowest specificity (74% and 66.7%) among this group. The inconsistency may be due to the risk of systematic error inherent from incompleteness of monitoring NES in one study¹⁶ and less stringent criterion for abnormal PRL in another¹⁴ (see table 1). To increase statistical power, we pooled the available data of Class I and Class II studies in the weighted average analysis. For the diagnosis of GTC or CPS, the pooled specificity ranged from 95.9 to 96.3%, whereas the pooled sensitivities were limited to 46.1 to 60.0% (table 2).

Applying Bayes' theorem, table 3 illustrates how the PRL predictive value depends on the pretest probability of ES in the population studied.¹¹ Assuming an ES pretest probability of 95% in the general epilepsy population, a positive PRL measure is highly predictive ($>99\%$) of either GTC or CPS. Even with an ES pretest probability as low as 50%, a positive PRL measure is still highly predictive of either GTC or CPS (positive predictive value of about 93%). By contrast, because of the relatively low sensitivity of the test, a negative PRL measure is not predictive of psychogenic NES and hence does not rule out a diagnosis of an ES.

Two Class II studies^{14,19} examined the time course of PRL attenuation following ES. In one study,¹⁹ 6 patients with ES had attenuation of mean PRL concentration to $17.5 \pm 3.6\%$ of mean peak postictal PRL by 2 hours after seizures. The 2-hour postictal PRL levels were similar to the baseline PRL measured at the same time on the subsequent seizure-free day. In another study,¹⁴ 32 patients with ES had postictal PRL elevation up to 6 hours ($p = 0.048$) when compared with the baseline PRL level.

Conclusions. On the basis of one Class I and seven Class II studies, an elevated PRL level when measured 10 to 20 minutes after a suspected event is *probably* a useful adjunct to differentiate GTC or CPS from psychogenic NES among adults and older children. On the basis of consistent Class I and II studies, a normal serum PRL assay by itself is insufficient to make a diagnosis of psychogenic NES or to exclude the possibility of GTC or CPS because of its low sensitivity and low negative predictive value. On the basis of two Class II studies, serum PRL, when measured more than 6 hours after an ES, is *probably* representative of the baseline PRL level.

Table 1 Prospective controlled studies investigating PRL changes following either ES or psychogenic NES

Reference	Patients, n	Age range, y	Reference standard	Lapse time of PRL measure, min	Criterion for elevated PRL	Class
Willert et al. ¹⁴	44	18–62	Video-EEG	20*	>16.5 ng/mL (male) [†] >23 ng/mL (female)	II
Shah et al. ¹⁵	89	Not provided	Video-EEG	Average = 15–20	2 × baseline level	II‡
Alving ¹⁶	58	13–68	Video and/or ambulatory cassette EEG	15	2 × baseline level at 2 h post event	II§
Ehsan et al. ¹⁷	50	6–61	Video-EEG	15	2 × baseline level at 1 h post event	II¶
Fisher et al. ¹⁸	20	>18	Video-EEG	10–20	>36 ng/mL	II
Rao et al. ¹⁹	12	13–47	Video-EEG	Immediately, then every 15 min × 2 h	At least 2 × baseline level	II
Wroe et al. ²⁰	33	15–73	Video-EEG	10	>45 ng/mL	II
Laxer et al. ²¹	70	9–54	Video-EEG	<20	Discriminant function	I
Pritchard et al. ²²	12	Not provided	Continuous EEG (± video)	15	2 × baseline level	II
Oxley et al. ²³	18	Not provided	Continuous EEG (Medilog 4-cassette recorder)	<20	>36 ng/mL	II

* Serum prolactin (PRL) levels were measured at 10, 20, 30, and 60 minutes and at 6, 12, and 24 hours post event. For consistency of presentation, data collected at 20 minutes post event were analyzed in this review.

[†] Lowest cutoff criterion for abnormal PRL among the studies in this group.

[‡] Data collected prospectively but analyzed retrospectively. Despite wide spectrum of patients, we downgraded the study to Class II given risk of expectation bias.

[§] EEG corroborated diagnosis reported for 17 of 20 nonepileptic seizure (NES) patients (85%). Twelve NES patients had multiple events studied, but the proportion of monitored patients was not provided. One NES patient was excluded from validity analysis because of absence of baseline PRL level. We downgraded the study to Class II because of the unclear number of unmonitored NES.

[¶] Diagnostic accuracy of capillary blood PRL levels measured by a modified immunoradiometric assay.¹⁷ Serum and capillary blood PRL values correlated with a Pearson coefficient of 0.92. We downgraded the study to Class II given additional risk of systemic error (instrument bias) and restricted availability of the immunoradiometric assay.

^{||} Not explicitly specified by author, and based upon interpretation of figures in the article.

ES = epileptic seizure; Lapse time of PRL measure = time elapsed from start of event until blood draw for PRL assay.

Question 2: Does serum PRL measure change following other neurologic conditions? **Syncope.** Two Class II studies investigated serum PRL changes during 60° head-up tilt-table test in subjects at risk of syncope (table 4). In one study of subjects with a mean age of 70 years,⁷ 11 syncopal subjects showed an elevated mean PRL level of 44 ng/mL (95% CI 27 to 61) when tested within 5 minutes of syncope, compared with a mean baseline PRL level of 10 ng/mL (95% CI 7 to 14). Ten nonsyncopal subjects showed no significant PRL change following head-up tilt. In another study of younger subjects (mean age approximately 30 to 40 years),⁸ 14 syncopal subjects showed a mean PRL level of 18.1 ng/mL at 5 to 10 minutes after syncope. This was more than twice their mean baseline PRL level of 7.7 ng/mL. This relative increase was significant compared with the relatively unchanged baseline and postevent PRL mean measures of 22 nonsyncopal subjects ($p < 0.004$). A mean PRL level of 18.1 ng/mL is high, but not clearly abnormal. The reasons for the difference of effect size are unclear and may reflect differences in age and PRL assay of the two studies.

Conclusion. On the basis of limited Class II studies, serum PRL possibly increases from baseline level when measured within 10 minutes after syncope in

adults. An elevated PRL level cannot be used to differentiate between seizure and syncope.

Repetitive seizures. One Class II study²⁴ measured serum PRL level within 20 minutes following termination of monitored SE among 15 patients (table 5). All post-SE PRL measures were within normal range and were in fact lower than baseline measures in most of the 15 patients. Two Class II studies prospectively investigated serum PRL measures following repetitive, discrete seizures (not SE), using video-EEG as a reference standard^{25,26} (see table 5). Postictal PRL rise was reduced when seizures occurred after short seizure-free intervals of less than 25 hours, compared with those occurring after longer seizure-free intervals.²⁵ In contrast, another study²⁶ showed that following repetitive seizures (mean 3 hours and 32 minutes apart), postictal PRL measures were markedly and consistently increased in 5 of 14 patients studied, regardless of the time interval between seizures. None of the 14 patients showed a decrease in postictal PRL measure. The reasons for the inconsistency of the data are unclear, although sample sizes were small in both studies, reflecting low statistical power.

Conclusions. On the basis of inconsistent studies, no conclusion can be established regarding se-

Table 2 Validity measures of serum PRL assay in differentiating ES from NES

Reference	No. ↑ PRL/no. seizures studied by type	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Willert et al. ¹⁴	All ES—28/32	87.5 (71.9–95.0)	66.7 (39.1–86.2)
	NES—4/12	—	—
Shah et al. ¹⁵	GTC—17/36	47.2 (32.0–63.0)	98.2 (90.4–99.7)
	CPS—19/56	33.9 (22.9–47.0)	98.2 (90.4–99.7)
	SPS—3/27	11.1 (3.9–28.1)	98.2 (90.4–99.7)
	NES—1/55	—	—
Alving ¹⁶	GTC—?	93 (NA)	74 (NA)
	CPS—?	61 (NA)	74 (NA)
	SPS—?	?	?
	NES—9/44	—	—
	All ES—?	69 (NA)	74 (NA)
Ehsan et al. ¹⁷	GTC—10/13	76.9 (49.7–91.8)	85.7 (60.1–96.0)
	CPS—15/17	88.2 (65.7–96.7)	85.7 (60.1–96.0)
	SPS—0/6	0 (0–39.0)	85.7 (60.1–96.0)
	NES—2/14	—	—
Fisher et al. ¹⁸	GTC—5/9	55.6 (26.7–81.1)	100 (51.0–100)
	CPS—1/7	14.3 (2.6–51.3)	100 (51.0–100)
	NES—0/4	—	—
Rao et al. ¹⁹	GTC—2/2	100 (34.2–100)	100 (56.6–100)
	CPS—3/4	75.0 (30.1–95.4)	100 (56.6–100)
	NES—0/5	—	—
Wroe et al. ²⁰	GTC—6/8	75.0 (40.9–92.9)	100 (72.3–100)
	CPS—5/11	45.5 (21.3–72.0)	100 (72.3–100)
	Absence—0/4	0 (0–49.0)	100 (72.3–100)
	NES—0/10	—	—
Laxer et al. ²¹	All ES—40/61	65.6 (53.1–76.3)	94.4 (74.2–99.0)
	NES—1/18	—	—
Pritchard et al. ²²	GTC—1/1	100 (20.7–100)	100 (61.0–100)
	CPS—5/5	100 (56.6–100)	100 (61.0–100)
	NES—0/6	—	—
Oxley et al. ²³	GTC—4/6	66.7 (30.0–90.3)	90.0 (59.6–98.2)
	CPS—0/4	0 (0–49.0)	90.0 (59.6–98.2)
	NES—1/10	—	—
		Pooled* sensitivity, %	Pooled* specificity, %
	All GTC† =	60.0 (48.9–71.1)	95.9 (91.4–100)
	All CPS† =	46.1 (36.5–55.7)	96.3 (92.7–99.9)
	All ES‡ =	52.6 (47.0–58.2)	92.8 (89.9–95.7)

* Pooled sensitivity calculated from weighted average of sensitivity values from Class I and Class II studies combined. Specificities were similarly pooled.

† Excluding the studies of Willert et al.,¹⁴ Alving et al.,¹⁶ and Laxer et al.,²¹ given data not provided.

‡ “All ES” includes data of all epileptic seizure types reported (generalized tonic-clonic seizures [GTCs], complex partial seizures [CPSs], simple partial seizures [SPSs], and absence seizures) from all studies except the study of Alving et al.¹⁶

PRL = prolactin; ES = epileptic seizure; NES = nonepileptic seizure; ? = not provided; NA = cannot be calculated from available data.

rum PRL changes following termination of SE. On the basis of conflicting Class II studies, no conclusion can be established regarding serum PRL changes following repetitive seizures (not SE).

Neonatal population. Two Class II studies prospectively assessed serum PRL changes following EEG-corroborated seizures among neonates^{27,28} (table 6). In one study,²⁷ neonates with electrographic

Table 3 Predictive values of serum PRL assay in relation to prevalence of NES

Pretest probability of ES,* %	PPV of serum PRL assay, %	NPV of serum PRL assay, %
For generalized tonic-clonic seizures only†, assuming specificity = 95.9% and sensitivity = 60.0%		
99	99.9	2.4
95	99.6	11.2
90	99.3	21.0
75	97.8	44.4
50	93.6	70.6
For complex partial seizures only†, assuming specificity = 96.3% and sensitivity = 46.1%		
99	99.9	1.8
95	99.6	8.6
90	99.1	16.6
75	97.4	37.3
50	92.6	64.1

* The pretest probability that an event is epileptic.

† Data unavailable from the studies of Willert et al.,¹⁴ Alving et al.,¹⁶ and Laxer et al.²¹

PRL = prolactin; NES = nonepileptic seizure; ES = epileptic seizure; PPV = positive predictive value; NPV = negative predictive value.

seizures showed an elevated mean ratio (2.71) of postictal PRL value over baseline value. This change was significant compared with PRL levels in neonates experiencing events without EEG correlate ($p = 0.037$). Postictal-to-baseline PRL ratios greater than 2 demonstrated a sensitivity of 45% and a specificity of 100% in diagnosing EEG-corroborated seizures. Patients with elevated postictal PRL ratios had overt focal tonic seizures, whereas 2 patients with subclinical seizures did not demonstrate PRL elevation. Another study²⁸ showed that among 6 patients with electrographic seizures, postictal PRL

values at 15 and 30 minutes were not statistically different compared with baseline values. However, 5 of 6 patients in this study had only subclinical seizures, and all of the ictal patients had moderate to severe EEG background abnormalities. Neonatal encephalopathy may be associated with elevated baseline PRL,²⁸ as well as absence of the postictal PRL surge relative to the baseline level.²⁷ The divergence of data may therefore be explained by systematic patient differences.

Conclusion. On the basis of conflicting Class II studies, no conclusion can be established regarding serum PRL changes following ES in neonates.

Discussion. Using either relative or absolute PRL rise as the criterion of abnormality, the pooled data suggest that elevated serum PRL is specific for differentiating CPS or GTC from psychogenic NES. The clinical utility of serum PRL arises from the high positive predictive value of the assay for ES. In the clinical setting, where GTC or CPS-like events are suspected to be psychogenic NES and where “organic” imitators such as syncope have been excluded, an elevated serum PRL supports an epileptic etiology. A positive test can therefore be clinically useful, especially in the hospital setting, where video-EEG monitoring is not readily available. It is important to recognize several limitations of the PRL assay. Data were insufficient to establish the predictive value of PRL following seizure types other than GTC and CPS. The low sensitivity of the assay implies that a negative test result is of little value in making the diagnosis of nonepileptic events. Furthermore, it is common for psychogenic NES to mimic repetitive seizures or SE, but data supporting the use of PRL in these settings are inconclusive. Epileptic and nonepileptic events may coexist in the same patient. Serum PRL helps only in the diagnosis of individual events rather than an epilepsy syndrome. PRL can rise after syncope, and it remains unknown whether PRL also rises following migraines, transient ischemic attacks, cardiac arrhythmias, and other organic imitators of epilepsy. Paired measurements of baseline and postictal PRL can help to discriminate condi-

Table 4 Methodologic characteristics of studies evaluating serum prolactin changes following tilt-induced syncope

Reference	Syncopal patients, n	Age, mean, y	Reference standard	Lapse time of PRL measure	Criterion for elevated PRL	Mean postsyncopal PRL, ng/mL	Mean baseline PRL of syncopal patients, ng/mL	Class
Oribe et al. ⁷	11	70	Documented BP drop and syncopal symptoms induced by tilt-test	<5 min	19 ng/mL	44 (95% CI 27-61)*	10 (95% CI 7-14)*	II
Theodorakis et al. ⁸	14	30-40	Syncopal symptoms induced by tilt-test	5-10 min	Not specified	18.1†	7.7†	II

* Among the 21 patients studied, head-up tilt triggered hypotension with syncope in 11 patients. For the 10 nonsyncopal patients, their mean post-tilt prolactin (PRL) level was 8 ng/mL (95% CI 6-10), compared with their mean baseline level of 7 ng/mL (95% CI 5-8).

† Fourteen patients developed syncopal symptoms. The increase in mean postsyncopal PRL level relative to mean baseline level was significant compared with the mean measures in 22 nonsyncopal subjects ($p < 0.004$).

BP = blood pressure measured via automatic sphygmomanometer.

Table 5 Methodologic characteristics of studies evaluating serum PRL changes following SE, or repetitive seizures (not SE)

Reference	Patients, n	Age, y	Reference standard	Lapse time of PRL measure	Criterion for elevated PRL	Postictal PRL	Class
Tomson et al. ²⁴	15	31–79	Ictal EEG recording	<20 minutes after termination of SE	>25 ng/mL	0/15*	II
Malkowicz et al. ²⁵	8	12–44	Video-EEG recording	At 15 minutes	>3 × baseline level	1.015(SFI) + 33.58†	II
Bauer et al. ²⁶	14	16–43	Video-EEG recording	At 5-, 30-, and 120-minute intervals	>32 ng/mL for females >23 ng/mL for males	5/14‡	II

* Out of 15 patients who sustained status epilepticus (SE), none demonstrated postictal prolactin (PRL) elevation.

† The regression equation for predicting 15-minute postictal PRL level as a function of seizure-free interval (SFI), with Pearson coefficient = 0.89. This indicates a low 15-minute postictal PRL value for seizures with short SFIs.

‡ Five of 14 patients showed marked PRL rise after first and each subsequent seizure. Mean SFI = 5 hours and 4 minutes.

tions associated with hyperprolactinemia such as pregnancy, lactation, prolactinomas, primary hypothyroidism, drugs (e.g., phenothiazines, bromocriptine), and several others. Failure to exclude these conditions can be expected to reduce the specificity of the PRL assays for the correct identification of ES.

The sensitivity and specificity of a diagnostic test is a function of the selected criteria of abnormality. There is always a trade-off between sensitivity and specificity depending on the cutoff point chosen, as is displayed in the receiver operator characteristic (ROC) curve. Some discrepancies among the studies reviewed may be related to differences in the chosen cutoff point. Given the lack of standardized criteria for an “abnormal” PRL measure, it is unknown whether the chosen criteria of the studies reflect the ideal sensitivity/specificity trade-off. This uncertainty represents a key limitation of current evidence, especially considering the discrepant high specificity and low sensitivity of PRL assay used to diagnose seizures. Nevertheless, the high specificity in a screening test ensures a low false-positive rate.

The studies reviewed suggest that serum PRL sampling should take place 10 to 20 minutes after the event. This timing generates significant logistical problems in using this test out of the hospital set-

ting. Methods can be developed for home acquisition of PRL samples,¹⁸ with testing later in specially equipped laboratories.

Practice recommendations: For clinicians considering a laboratory blood test to diagnose ES

1. Elevated serum PRL, when measured in appropriate clinical setting at 10 to 20 minutes after a suspected event, should be considered a useful adjunct to differentiate GTC or CPS from psychogenic NES among adults and older children (Level B).
2. Serum PRL, when measured more than 6 hours after a suspected event, should be representative of the baseline PRL level (Level B).
3. Serum PRL assay is not of utility to distinguish seizure from syncope (Level B).
4. The utility of serum PRL assay has not been established in the evaluation of SE, repetitive seizures, or neonatal seizures (Level U).

Recommendations for future research. *Standardization of “abnormal” PRL elevation.* A large-sample-size, gender-matched study of baseline PRL values in healthy and epileptic subjects, allowing for uninterrupted sleep, may provide more accurate

Table 6 Methodologic characteristics of studies evaluating serum PRL changes following neonatal seizures

Reference	Patients, n	GA, wk/PNA, d	Reference standard	Lapse time of PRL measure	Criteria for elevated PRL	Seizure group	Nonseizure group	Class
Morales et al. ²⁷	19	39.2/10.5	2-hour EEG	30 minutes	>2 × baseline	5/11*	0/8*	II
Legido et al. ²⁸	28	38.4/3.9	40-minute EEG	15 minutes and 30 minutes	Not specified	Mean postictal PRL = 175 ng/mL† at 15 minutes, 188 ng/mL† at 30 minutes	Mean PRL = 114 ng/mL at end of EEG study	II

* Postictal prolactin (PRL) increased >2 × baseline value in 5 of 11 patients with EEG seizures (mean PRL ratio = 2.71) and in 0 of 8 patients without EEG seizures (mean PRL ratio = 1.26). The PRL ratios were significantly higher in the seizure group ($p = 0.037$).

This criterion diagnosed neonatal seizures with a sensitivity of 45% and a specificity of 100%. Among the 11 patients with EEG seizures, 2 had subclinical seizures.

† Not significant compared with the mean baseline PRL value (170 ng/mL) of the seizure group.

GA = gestational age; PNA = postnatal age.

standardization of gender-specific PRL threshold values. Because sensitivity and specificity parameters depend on the cutoff points chosen, the use of a ROC curve may allow for the choice of the proper sensitivity/specificity trade-off.

Capillary PRL assays. Capillary PRL assay using a “finger-stick” methodology can be as accurate as venous PRL assay in differentiating ES from psychogenic NES.^{17,18} Future studies investigating the utility of an outpatient PRL kit kept at home to document capillary PRL changes shortly post event may circumvent current practical limitations.

PRL in other types of organic nonepileptic events. With the exception of syncope, little is known regarding serum PRL changes following other seizure imitators that may affect the hypothalamic–pituitary axis. Such organic imitators include migraine, transient ischemic attacks, cardiac arrhythmias, transient global amnesia, and others. Future studies are necessary to define the specificity of PRL assay in the setting of these events.

Pediatric population. We reviewed several Class II studies that included children as young as 6 years old.^{16,17,19–21} We did not find other controlled, prospective studies that studied infants or younger children using video-EEG monitoring. Utilization of serum PRL assay in neonates presents additional problems not evident in adults. Neonatal serum PRL concentration is highly dependent on gestational age²⁹ and postnatal age,³⁰ and may be influenced by coexisting encephalopathy.²⁸ Moreover, many neonatal electrographic seizures may be clinically occult,³¹ and some clinical seizures may not demonstrate electrographic correlation.³² Future prospective studies of postictal PRL measures in neonates and young children are needed.

PRL in other epileptic disorders. Further data are needed in order to interpret PRL value following SE and repetitive seizures.

Disclaimer. This assessment focused on the use of serum PRL assay in the diagnosis of ES. The utility of serum PRL assay in other indications is beyond the scope of this review. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix 1

Classification of evidence

Class I: Evidence provided by a prospective study in a broad spectrum of persons with the suspected condition, using a reference (“gold”) standard for case definition, where a test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy. All patients undergoing the diagnostic test have the presence or absence of the disease determined.

Class II: Evidence provided by a prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by “gold standard”) compared with a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where the reference standard, if not objective, is applied by someone other than the person who performed the test.

Class IV: Any design where the test is not applied in an independent evaluation or evidence provided by expert opinion alone or in descriptive case series (without controls).

Appendix 2

Classification of recommendations

- A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)
- B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)
- C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
- U = Data inadequate or conflicting given current knowledge; treatment is unproven.

Appendix 3

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References

1. Frantz AG. Prolactin. *N Engl J Med* 1978;298:201–207.
2. Parra A, Velasco M, Cervantes C, Munoz H, Cerborn MA, Velasco F. Plasma prolactin increase following electrical stimulation of the amygdala in humans. *Neuroendocrinology* 1980;31:60–65.
3. Trimble MR. Serum prolactin in epilepsy and hysteria. *BMJ* 1978;2:1682.
4. Cavallo A, Moore DC, Nahori A, Beaumanoir A, Sizonenko PC. Plasma prolactin and cortisol concentrations in epileptic patients during the night. *Arch Neurol* 1984;41:1179–1182.
5. Bauer J, Stefan H, Schrell U, Uhlig B, Landgraf S, Neubauer U, Neundorfer B, Burr W. 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. *Eur Arch Psychiatry Clin Neurosci* 1992;241:365–371.
6. Molaie M, Culebras A, Miller M. Nocturnal plasma prolactin and cortisol levels in epileptics with complex partial seizures and primary generalized seizures. *Arch Neurol* 1987;44:699–702.
7. Oribe E, Amini R, Nissenbaum E, Boal B. Serum prolactin concentrations are elevated after syncope. *Neurology* 1996;47:60–62.
8. Theodorakis GN, Markianos M, Livanis EG, Zarvalis E, Flevari P, Kremastinos DT. Hormonal responses during tilt-table test in neurally mediated syncope. *Am J Cardiol* 1997;79:1692–1695.
9. Cordingley G, Brown D, Dane P, Harnish K, Cadamagnani P, O'Hare T. Increases in serum prolactin levels associated with syncopal attacks. *Am J Emerg Med* 1993;11:251–252.
10. Lusic I, Pintaric I, Hozo I, Boic L, Capkun V. Serum prolactin levels after seizure and syncopal attacks. *Seizure* 1999;8:218–222.
11. Yerby MS, van Belle G, Friel PN, Wilensky AJ. Serum prolactins in the diagnosis of epilepsy: sensitivity, specificity, and predictive value. *Neurology* 1987;37:1224–1226.
12. Bauer J. Epilepsy and prolactin in adults: a clinical review. *Epilepsy Res* 1996;24:1–7.
13. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;17:857–872.

14. Willert C, Spitzer C, Kusserow S, Runge U. Serum neuron-specific enolase, prolactin, and creatine kinase after epileptic and psychogenic non-epileptic seizures. *Acta Neurol Scand* 2004;109:318–323.
15. Shah AK, Shein N, Fuerst D, Yangala R, Shah J, Watson C. Peripheral WBC count and serum prolactin level in various seizure types and nonepileptic events. *Epilepsia* 2001;42:1472–1475.
16. Alving J. Serum prolactin levels are elevated also after pseudo-epileptic seizures. *Seizure* 1998;7:85–89.
17. Ehsan T, Fisher RS, Johns D, Lukas R, Blum D, Eskola J. Sensitivity and specificity of paired capillary measurement in diagnosis of seizures. *J Epilepsy* 1996;9:101–105.
18. Fisher RS, Chan DW, Bare M, Lesser RP. Capillary prolactin measurement for diagnosis of seizures. *Ann Neurol* 1991;29:187–190.
19. Rao ML, Stefan H, Bauer J. Epileptic but not psychogenic seizures are accompanied by simultaneous elevation of serum pituitary hormones and cortisol levels. *Neuroendocrinology* 1989;49:33–39.
20. Wroe SJ, Henley R, John R, Richens A. The clinical value of serum prolactin measurement in the differential diagnosis of complex partial seizures. *Epilepsy Res* 1989;3:248–252.
21. Laxer KD, Mulooly JP, Howell B. Prolactin changes after seizures classified by EEG monitoring. *Neurology* 1985;35:31–35.
22. Pritchard PB, Wannamaker BB, Sagel J, Daniel CM. Serum prolactin and cortisol levels in evaluation of pseudoepileptic seizures. *Ann Neurol* 1985;18:87–89.
23. Oxley J, Roberts M, Dana-Haeri J, Trimble M. Evaluation of prolonged 4-channel EEG- taped recordings and serum prolactin levels in the diagnosis of epileptic and nonepileptic seizures. In: Dam M, Gram L, Penry JK, eds. *Advances in epileptology: XIIth Epilepsy International Symposium*. New York: Raven Press, 1981:343–355.
24. Tomson T, Lindbom U, Nilsson B, Svanborg E, Andersson DE. Serum prolactin during status epilepticus. *J Neurol Neurosurg Psychiatry* 1989;52:1435–1437.
25. Malkowicz DE, Legido A, Jackel RA, Sussman NM, Eskin BA, Harner RN. Prolactin secretion following repetitive seizures. *Neurology* 1995;45:448–452.
26. Bauer J, Kaufmann P, Klingmuller D, Elger CE. Serum prolactin response to repetitive epileptic seizures. *J Neurol* 1994;241:242–245.
27. Morales A, Bass NE, Verhulst SJ. Serum prolactin levels and neonatal seizures. *Epilepsia* 1995;36:349–354.
28. Legido A, Lago P, Chung HJ, Sperling M, Clancy RR. Serum prolactin in neonates with seizures. *Epilepsia* 1995;36:682–686.
29. Schober E, Simbruner G, Salzer H, Husslein P, Spona J. The relationship of prolactin in cord blood, gestational age and respiratory compliance after birth in newborn infants. *J Perinat Med* 1982;10:23–26.
30. Tapanainen J. Hormonal changes during the perinatal period: serum testosterone, some of its precursors, and FSH and prolactin in preterm and fullterm male infant cord blood and during the first week of life. *J Steroid Biochem* 1983;18:13–18.
31. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. *Epilepsia* 1988;29:256–261.
32. Mizrahi EM. Neonatal seizures: problems in diagnosis and classification. *Epilepsia* 1987; 28 Suppl 1: S46–S55.

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