

IS PROLACTIN A CLINICALLY USEFUL MEASURE OF EPILEPSY?

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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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).

COMMENTARY

The diagnosis of epilepsy is not always easy to establish. Seizures easily can be confused with other diagnoses, such as syncope, migraine, or transient ischemic attack, but they are most frequently confused with nonepileptic seizures of psychogenic origin. A positive EEG is the gold standard for establishing the diagnosis of epilepsy and, in some cases, for evaluating seizure type and syndrome. In contrast, a negative EEG finding does not rule out the diagnosis of epilepsy. The most reliable methodology is video-EEG registration. Unfortunately, not all neurologists or even epilepsy centers have access to video monitoring, so it would be very helpful to identify another surrogate measure of epilepsy.

Prolactin elevation in serum following seizure has been considered a potential candidate for a surrogate marker. The first study to evaluate the correlation between serum prolactin elevation and epilepsy was published in 1978 by Trimble (1), who showed that a generalized tonic-clonic seizure increased prolactin serum levels but psychogenic nonepileptic seizures did not. Since then, over 396 papers have addressed the general

topic of serum prolactin elevation and epilepsy. In the present paper, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated the evidence pertaining to prolactin as a marker for the occurrence of an epileptic seizure. They found 41 articles that satisfied the minimum requirements for controlled studies that analyzed prolactin changes in seizures or seizure-like events. The subcommittee addressed two main questions: (i) Is a serum prolactin assay useful in differentiating epileptic seizures from psychogenic nonepileptic seizures and (ii) Does serum prolactin measure change following other neurologic conditions?

As the abstract reveals, the subcommittee determined that data from eight studies (one Class I and seven Class II) were satisfactory to answer the first question regarding differentiating epileptic seizures from psychogenic nonepileptic seizures (2–10). On the basis of these studies, the subcommittee felt confident to conclude that if prolactin can be measured 10 to 20 minutes after an event, then it *probably* can be a useful measure to differentiate between a generalized tonic-clonic seizure or complex partial seizure and psychogenic nonepileptic seizures. However, if the serum prolactin test is taken 6 hours after the event, then it is *probably* indicative of the baseline prolactin level of that patient. A blood test that has to be taken 10 to 20 minutes after a seizure means that the patient would

have to have a seizure in front of a doctor or already be in the hospital, which obviously creates practical problems. Moreover, a normal prolactin level does not exclude a diagnosis of epilepsy or establish a diagnosis of psychogenic seizures because of its low assay sensitivity. Complicating matters even further, some patients with epilepsy also can have psychogenic seizures.

Regarding the second question on the specificity of prolactin elevation to diagnose seizure, only two Class II studies evaluated patients during head-up tilt table test (11,12). This is a test to induce and evaluate syncope in patients who are prone to fainting. Both studies found that prolactin levels were elevated more than double the baseline values within 5 to 10 minutes after syncope in patients compared to controls, who had levels largely unchanged from baseline. Thus, the conclusion of the subcommittee was that prolactin is *possibly* increased (up to 10 minutes after an attack) in adults with syncope.

What is known about repetitive seizures or status epilepticus and prolactin levels? The studies that have been performed were judged to be conflicting, and so no conclusion could be drawn as to whether prolactin levels increased during status or repetitive discrete (not generalized tonic-clonic) seizures. There were two studies carried out with neonates (13,14), but again no conclusions were reached, either because of conflicting results or because of patient characteristics that differed widely.

From the subcommittee analyses, one can conclude that there are many problems involved with prolactin measurements as a surrogate marker for seizure occurrence. It is important to know the patient's baseline prolactin value before concluding that the level is significantly elevated, but this issue can be solved by taking the baseline value 6 hours after the seizure and use the acute level as a comparison. For other diagnostic dilemmas, such as migraine or transient ischemic attack, it is not known if prolactin is a useful surrogate marker or not.

The study discloses that there are too few adequate Class I or Class II studies to definitively conclude whether prolactin is useful or not, that is, except in differentiating between epilepsy and psychogenic nonepileptic seizures, which then becomes the primary area of importance. The main advantage of using prolactin as a surrogate marker is that the physician can be fairly sure that if the prolactin level is increased after an event, it is probably epilepsy or syncope. If the EEG shows epileptic activ-

ity, then a diagnosis could be established—but it would have been established without the prolactin analysis.

The search for other indicators of epilepsy continues.

by Elinor Ben-Menachem, MD, PhD

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