Seizure 22 (2013) 85–90

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

REVIEW

The diagnostic value of urinary incontinence in the differential diagnosis of seizures

Francesco Brigo [a,b,*], Raffaele Nardone [b,c], Harald Ausserer [b], Monica Storti [d], Frediano Tezzon [b], Paolo Manganotti [a], Luigi Giuseppe Bongiovanni [a]

[a] Department of Neurological, Neuropsychological, Morphological and Movement Sciences, Section of Clinical Neurology, University of Verona, Verona, Italy
[b] Department of Neurology, Franz Tappeiner Hospital, Meran/o, Italy
[c] Department of Neurology, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria
[d] Department of Medicine, University of Verona, Verona, Italy

ARTICLE INFO

Article history:
Received 17 September 2012
Received in revised form 19 October 2012
Accepted 20 October 2012

Keywords:
Epileptic seizures
Likelihood ratio
Meta-analysis
Psychogenic nonepileptic events
Sensitivity
Specificity
Syncope
Urinary incontinence

ABSTRACT

Purpose: Urinary incontinence may occur both in epileptic seizures (ES) and in non-epileptic events (NEE) such as psychogenic nonepileptic events (PNEEs) and syncope. A comprehensive search of the literature to determine the accuracy of this physical finding and its prevalence in epileptic seizures and syncope is still lacking.

To undertake a systematic review to determine sensitivity, specificity and likelihood ratios (LR) of urinary incontinence in the differential diagnosis between ES and NEEs (including syncope and PNEEs).
Methods: Studies evaluating the presence of urinary incontinence in ES and NEEs were systematically searched. Sensitivity, specificity, positive and negative likelihood ratio (pLR, nLR) of incontinence were determined for each study and for the pooled results.
Results: Five studies (221 epilepsy patients and 252 subjects with NEEs) were included. Pooled accuracy measures of urinary incontinence (ES versus NEEs) were: sensitivity 38%, specificity 57%, pLR 0.879 (95% CI 0.705–1.095) and nLR 1.092 (95% CI 0.941–1.268). For each comparison (epileptic seizures versus NEEs; ES versus syncope; ES versus PNEEs), pooled accuracy measures for urinary incontinence showed a statistically not significant pLR (the 95% CI of the pooled value included 1, and the LR value of 1 has no discriminatory value).
Conclusions: A pooled analysis of data from the literature shows that urinary incontinence has no value either in the differential diagnostic between ES and syncope/PNEEs. Systematic reviews with pooled analyses of data from the literature allow an increase in statistical power and an improvement in precision, representing a useful tool to determine the accuracy of a certain physical finding in the differential diagnosis between ES and other paroxysmal events.

1. Introduction

Paroxysmal episodes of loss of consciousness are rarely witnessed by physicians, and the differential diagnosis between epileptic seizures (ES) and other episodes is usually based on the history. However, even with an accurate description by witnesses, the diagnosis may be difficult and often remains uncertain.[1] In the differential diagnosis of paroxysmal episodes of loss of consciousness one should mainly consider ES, syncope and psychogenic nonepileptic events (PNEEs).

The diagnosis relies mainly on an accurate history or on a description of the event given by witnesses, and the presence or absence of physical signs may provide additional information to support or rule out the initial diagnostic suspicion. In previous systematic reviews we assessed the diagnostic value of tongue biting in the differential diagnosis between seizures and seizures and between PNEEs and seizures, concluding that in both cases the presence of tongue biting supports the diagnosis of epileptic seizures.[2,3]

The presence of urinary incontinence is an additional clinical sign which may occur both in patients with seizures and in subjects with non-epileptic events (NEEs). A comprehensive search of the literature to determine the accuracy of this physical finding

* Corresponding author at: Department of Neurological, Neuropsychological, Morphological and Movement Sciences, Section of Clinical Neurology, University of Verona, Piazzale L.A. Scuro, 10 – 37134 Verona, Italy. Tel.: +39 0458124174; fax: +39 0458124873.
E-mail address: dr.francescobrigo@gmail.com (F. Brigo).

1059-1311/$ – see front matter © 2012 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2012.10.011

(with special regards to its positive likelihood ratio) in the differential diagnosis between ES and NEEs has not yet been performed.

In this study we therefore aimed to undertake a systematic review to evaluate sensitivity, specificity and likelihood ratios (LR) of urinary incontinence in the differential diagnosis between epileptic seizures and NEEs (syncope or PNEEs).

2. Methods

Our aim was to critically and systematically evaluate the literature to evaluate the sensitivity, specificity, positive LR (pLR) and negative LR (nLR) of urinary incontinence in the differential diagnosis between epileptic seizures and NEEs (syncope or PNEEs).

We included prospective and retrospective studies comparing the presence of incontinence between patients with ES (all types) and patients with NEEs. No race or gender restrictions were applied. Studies could rely on historical reports of incontinence from patients, on direct examination of patients who presented to the emergency unit following a seizure, or on video-EEG monitoring evaluation.

Studies not reporting the frequencies of occurrence of urinary incontinence for each patient group (expressed as per patient or per event frequencies) were excluded.

The MEDLINE (accessed by Pubmed; 1966–May 2012) electronic database was searched using the following medical subject headings (MeSH): "Epilepsy", "Seizures" and "Urinay incontinence", as well as following free terms, combined in multiple search strategies with Boolean operators in order to find relevant articles: "incontinence", "incont", "epileps*", "epilept*", "seizur*" (see "Appendix"). Abstracts were reviewed to determine which full-text articles should be retrieved. In addition, reference lists from each of the articles that were included in the review were manually searched for papers meeting the inclusion criteria and not identified through MEDLINE. Papers were eligible for inclusion if they assessed urinary incontinence, if the frequencies of occurrence of ictal signs were reported for all patient groups or if it was possible to calculate them from the given data. Case reports were not included. Studies were excluded if they were conducted on a paediatric population.

In order to provide a transparency of results as great as possible, and to allow readers to reproduce the methodology we adopted, and considering that in abstracts many methodological aspects are not declared and results are often synthesized, only in-extenso in extenso papers and articles already published were considered eligible for inclusion.

The methodological quality of each study was evaluated. The methodological quality of each study was evaluated using the following criteria[4]: (1) independent, blind comparison with a valid test ("gold" or reference diagnostic standard, i.e. presence of urinary incontinence assessed by a physician or reported by patients); (2) patient sample including an appropriate spectrum of patients to whom the diagnostic test can be applied in clinical practice; (3) results of the physical sign being evaluated (i.e. presence of urinary incontinence) not influencing the decision to

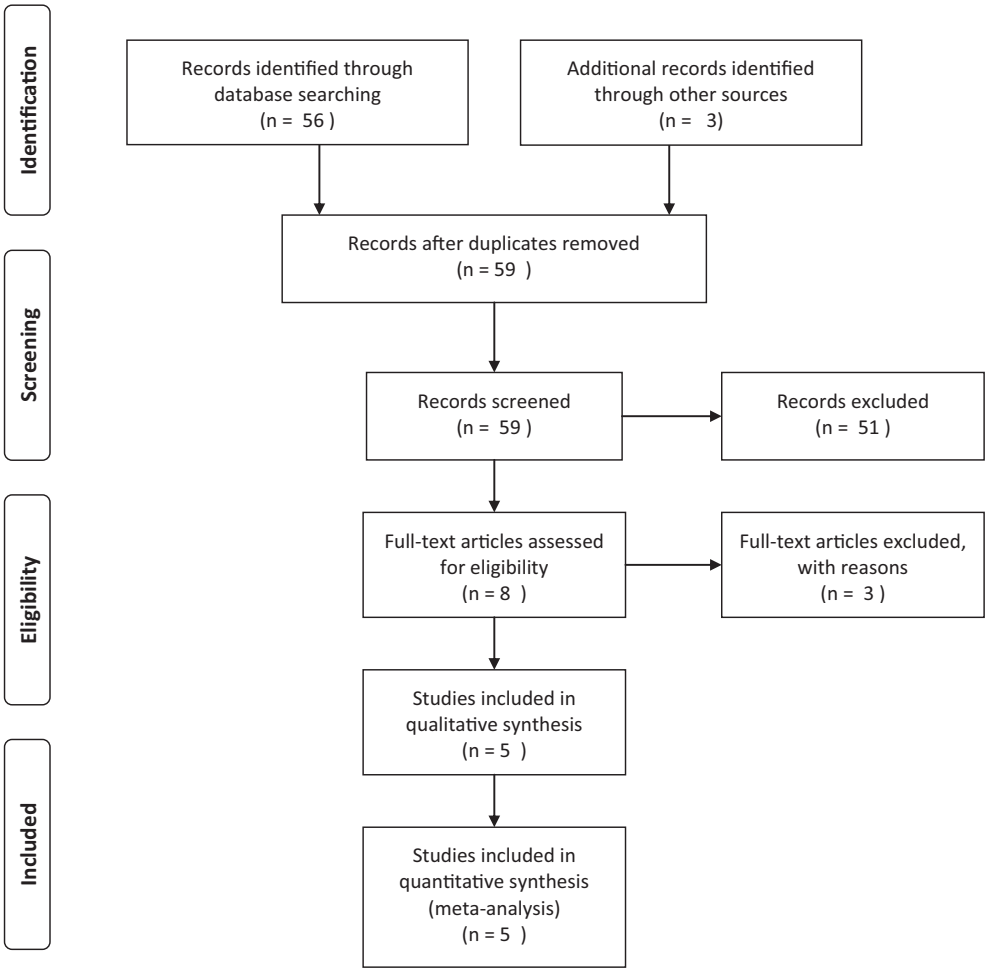

Fig. 1. Flowchart of study selection and inclusion.

perform the reference diagnostic standard; (4) description of physical sign in sufficient detail to permit replication.

Provided we thought it clinically appropriate, and no important clinical and methodological heterogeneity was found, we determined pooled accuracy measures.

Sensitivity, specificity, pLR and nLR with 95% CIs were determined for each included study and for the summary estimate of pooled analysis using equations reported in Appendix.[5–7]

Subgroup analyses assessing accuracy measures of urinary incontinence in the differential diagnosis between ES and syncope and between ES and PNEEs were performed.

Stats calculator available at: http://ktclearinghouse.ca/cebm/practise/ca/calculators/statscalc was used to calculate accuracy measures.

3. Results

The search strategy described above yielded 59 results (56 MEDLINE, 3 in reference lists).

After reading the abstracts, eight studies were provisionally selected. After reading the full text of the retrieved articles, 5 studies were included (Fig. 1).

Thus 5 studies, comprising 221 epilepsy patients and 252 subjects with NEEs, contributed to this review.[8–12]

3.1. Assessment of methodological quality of included studies (Table 1)

Only one prospective study reported data on urinary incontinence in patients with syncope.[8] This study performed the same diagnostic tests both in patients with ES and in patients with syncope, although it was not specified whether all instrumental tests (e.g. 24 h cardiac monitoring, tilt table) were performed in all patients with suspected syncope (partial verification bias). Moreover, in this study it was not specified whether the presence of urinary incontinence was evaluated independently from and blind to the definite diagnosis. Based on the information provided on this study, the spectrum of patients with ES included predominantly patients with motor phenomena, although the spectrum of patients with syncope was wide (i.e. including patients with vasovagal syncope or syncope occurring after hyperventilation, micturition/cough; low risk of representative spectrum bias).

A video-EEG recording of the paroxysmal event ideally represents the reference (“gold”) standard in the differential diagnosis between ES and PNEEs. In all included studies focusing on patients with ES and PNEEs a clinical evaluation was performed by epileptologists working in tertiary epilepsy centres and applied both to all patients. Although not all studies used an ictal video-EEG recording in patients with ES, in all subjects with PNEEs was obtained a video-EEG recording of the paroxysmal events.

In all studies focusing on ES and PNEEs except from that of Brown et al.[9] and Oliva et al.[12] it was not specified whether the presence of urinary incontinence was evaluated independently from and blind to the definite diagnosis. Two studies were prospective,[9,12] whereas two studies obtained data retrospectively from hospital records and postal/telephone questionnaires.[10,11]

Based on the information provided from studies focusing on PNEEs and ES, it is difficult to evaluate whether the spectrum of patients with ES was sufficiently large to include both patients with and without motor phenomena, although it is possible that patients with motor phenomena were selectively/predominantly included (such as in the study of Oliva et al.[12]; risk of representative spectrum bias).

The choice of an appropriate spectrum of patients may have great influence on accuracy measures. For instance, considering

Table 1
Description of included studies.

Study	Group	Inclusion criteria	Exclusion criteria	Number of subjects, male/female	Age	Type of seizures/NEEs	Diagnostic reference used	Type of study, information on UI
Hoefnagels et al.[8]	ES	Patients with one or more episodes of transient loss of consciousness. Transient loss of consciousness was defined as an episode of less than 1 h with inability to maintain posture, loss of contact with the environment, and amnesia for the events which occurred during the episode.	Loss of consciousness due to trauma or subarachnoid haemorrhage. Patients known to suffer from epilepsy.	41, 24/17	36 (SD 18)	35 clonic movements; 4 automatism, 2 motionless with aura. Final diagnosis: 7 generalized epilepsy; 14 partial epilepsy; 20 single seizure.	Clinical evaluation and assessment of data provided by the eyewitness and the patient. General and neurological examination, routine laboratory tests, EEG, ECG. Cerebral CT scan or 24 h cardiac monitoring (when considered necessary).	Prospective, data obtained by clinical evaluation and assessment of data provided by the eyewitness and the patient. Not reported whether UI assessment was made independently and blinded to the diagnosis.
	Syncope			53, 24/29	52 (SD 22)	2 clonic movements; 15 other movements; 36 motionless with aura. Final diagnosis: 11 vasovagal syncope; 14 hyperventilation; 3 micturition/cough; 3 cardiac syncope; 2 vertebrobasilar TIA; 1 postural hypotension; 19 unexplained.		

Table 1 (*Continued*)

Study	Group	Inclusion criteria	Exclusion criteria	Number of subjects, male/female	Age	Type of seizures/NEEs	Diagnostic reference used	Type of study, information on UI
Brown et al.[9]	ES	–	–	25[a], 9/16	(range 18–46)	12 primary generalized tonic-clonic seizures; 12 complex partial seizures; 1 simple partial seizures.	Epileptic EEG abnormalities documented by two electroencephalograohers on at least two EEGs.	Prospective, data obtained from interview data and video recording. Examiners were blind to subjects's diagnoses.
	PNEE	Attacks similar to those reported by history, in absence of ictal interictal, or postictal EEG abnormalities.	Equivocal interictal EEG recordings.	23, 5/18	(range 19–59)		Ictal video-EEG	
Peguero et al.[10]	ES	–	–	30, 10/20	29 (range 7–56)	27 partial epilepsy (complex partial with/ without generaluzation); 3 generalized epilepsy (2 myoclonic and tonic-clonic seizures, 1 tonic and atypical absence seizures)	Ictal video-EEG	Retrospective, data obtained using a telephone interview. Not reported whether UI assessment was made independently and blinded to the diagnosis.
	PNEE	Attacks recorded with video-EEG and considered typical by relatives who had witnessed the events.	Events characterized only by a subjective experience, a subtle motor activity, or behavioural change in infants or children; epileptic seizures of mesio-frontal origin.	73, 17/56	32 (range 9–52)			
Reuber et al.[11]	ES	–	Evidence of concurrent PNEE.	64, 40/24	38.8 (SD 10.1)	–	Ictal EEG or video-EEG; clinical assessment of an experienced epileptologist.	Retrospective, data extracted from hospital records and a postal questionnaire. Not reported whether UI assessment was made independently and blinded to the diagnosis.
	PNEE	Documentation of spontaneous psychogenic events with video-EEG, EEG, seizure observation and ictal examinations, clinical assessment of an experienced epileptologist, or provocation of a typical event by intravenous injection of 0.9% saline unde video-EEG. Multiple admissions to hospital.	Evidence of concurrent epilepsy; epileptiform potentials in interictal EEGs.	85, 15/70	37.1 (SD 15.8)	33 history of seizures lasting over 30 min leading to more than one hospital admission; 52 subjects without history of seizures lasting over 30 min.		
Oliva et al.[12]	ES	Occurrence of at least one convulsive event, defined clinically as one that involved simultaneous shaking of the body including all limbs.	–	66, 35/31	37.4 (SD 1.7)	36 temporal lobe epilepsy; 15 extratemporal lobe epilepsy; 15 primary generalized epilepsy.	Ictal video-EEG, clinical and investigational findings.	Prospective, direct documentation of UI. Information regarding UI was gathered independently and blinded to the diagnosis.
	PNEE		–	18, 7/11	40.4 (SD2.7)	–		

ES, epileptic seizures; PNEE, psychogenic non-epileptic events; SD, standard deviations; UI, urinary incontinence; –, not reported.

[a] Data from one patient missing.

Table 2
Accuracy measurements for each study and for pooled results.

Urinary incontinence				
Study	Sensitivity (95% CIs)	Specificity (95% CIs)	pLR (95% CIs)	nLR (95% CIs)
Hoefnagels et al.[8]	17%	74%	0.646 (0.287–1.454)	1.127 (0.911–1.394)
Brown et al.[9]	20%	96%	4.6 (0.559–37.858)	0.836 (0.661–1.059)
Peguero et al.[10]	57%	56%	1.293 (0.861–1.941)	0.772 (0.489–1.218)
Reuber et al.[11]	52%	34%	0.783 (0.59–1.038)	1.42 (0.962–2.094)
Oliva et al.[12]	35%	67%	1.045 (0.503–2.173)	0.977 (0.674–1.417)
Pooled results (ES versus NEEs)	38%	57%	0.879 (0.705–1.095)	1.092 (0.941–1.268)
Pooled results (ES versus syncope, subgroup analysis)	17%	74%	0.646 (0.287–1.454)	1.127 (0.912–1.315)
Pooled results (ES versus PNEEs, subgroup analysis)	43%	52%	0.896 (0.717–1.12)	1.095 (0.911–1.394)

that urinary incontinence occurs in patients with generalized tonic–clonic seizures, adopting less strict inclusion criteria (i.e. including also non-motor ES) would decrease sensitivity of this physical sign, without affecting specificity.

More detailed characteristics of included studies are reported in Table 1.

3.2. Quantitative synthesis (Table 2)

1. Urinary incontinence in the differential diagnosis between ES and NEEs

   Sensitivity, specificity, pLR and nLR of TB for the diagnosis of ES.

   Sensitivity, specificity, pLE and nLR for each included study are reported in Table 2.

   Pooled accuracy measures were: sensitivity 38%, specificity 57%, pLR 0.879 (95% CI 0.705–1.095) and nLR 1.092 (95% CI 0.941–1.268).
2. Urinary incontinence in the differential diagnosis between ES and syncope (Subgroup analysis)

   Sensitivity, specificity, pLR and nLR of TB for the diagnosis of ES.

   Sensitivity was 17%, specificity 74%, pLR 0.646 (95% CI 0.287–1.454) and nLR 1.127 (95% CI 0.911–1.394).
3. Urinary incontinence in the differential diagnosis between ES and PNEEs (Subgroup analysis)

   Sensitivity, specificity, pLR and nLR of TB for the diagnosis of ES

   Sensitivity, specificity, pLE and nLR for each included study are reported in Table 2.

   Pooled accuracy measures were: sensitivity 43%, specificity 52%, pLR 0.896 (95% CI 0.717–1.12) and nLR 1.095 (95% CI 0.912–1.315).

4. Discussion

The diagnosis of ES is primarily clinical and relies on patient's history and an accurate witness description of the attacks in the event of loss of awareness, consciousness, or recall of the events. Sometimes, a diagnosis of seizures may be supported by clinical findings, such as tongue biting or urinary incontinence.

A modern and evidence-based approach to the clinical diagnosis of seizures should take into account the concept of refining probability, an evidence-based technique which refines probability of an epileptic event, thus modifying the estimate of the likelihood of a disease through the application of a diagnostic test or the evaluation of a physical finding.[13,14] Refining probability represents therefore a clinical way of stating the Bayes' theorem: the probability of an event depends on new information applied to what is previously known about that event.

Likelihood ratios (i.e., information given by a test or by evaluation of a clinical sign) assess the discriminatory power of a diagnostic test. The LR for a positive test results (or for the presence of a physical finding) is the ratio of the chance of a positive results if the patient has a certain disease to the chance of a positive results if the patient does not have that disease.[2] For example, a LR of 2 for a positive results indicates that a positive result is twice as likely to occur in an individual with disease than in one without it.

In this systematic review, we used systematic and explicit methods to identify, select and critically appraise studies, and to extract data, analysing them with a meta-analysis. A meta-analysis is the statistical combination of results from two or more separate studies (pair-wise comparisons of interventions), allowing an increase in statistical power, an improvement in precision,

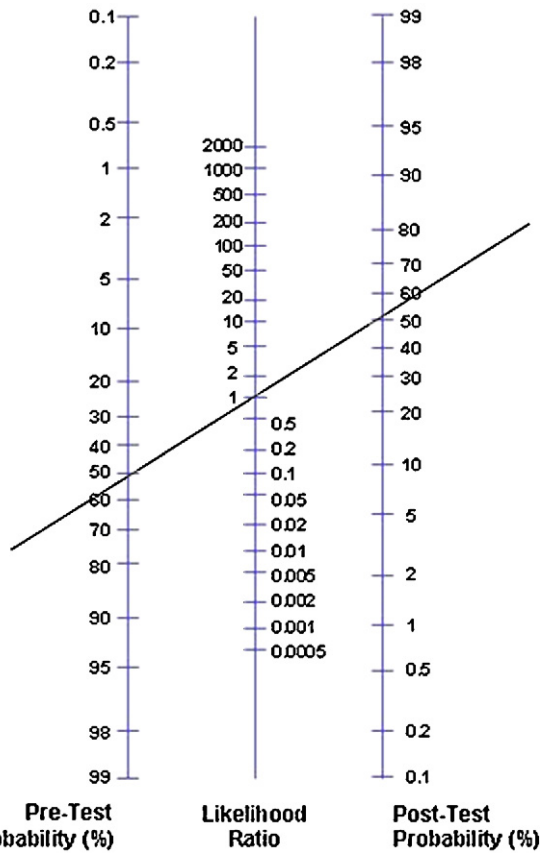

Fig. 2. The probability of ES is estimated by means of a nomogram describing how pre-test probability relates to post-test probability given the LR for incontinence. Given the same pre-test probability of seizures (i.e. prevalence) of 50%, the presence of urinary incontinence does not increase the chance that the patient had an ES (continuous line) (pLR = close/equal to 1).

sometimes permitting to answer questions not posed by individual studies and to settle controversies arising from conflicting claims.

For each comparison pooled accuracy measures for urinary incontinence showed a statistically not significant pLR (the 95% CI of the pooled value included 1, and the LR value of 1 has no discriminatory value).

In fact, if the probability of ES is estimated by means of a nomogram describing how pre-test probability relates to post-test probability given the LR for such a physical finding,[15] the chance that the patient had an ES appears not to be modified by the presence of urinary incontinence (Fig. 2).

It is possible that patients with motor phenomena were selectively/predominantly included in the primary studies, so that information on NEEs with pure sensory phenomena or unresponsiveness is scarce. Assessing the methodological quality of primary studies revealed several methodological shortcomings, the most relevant being the fact that the investigators who assessed the ictal signs were only rarely blinded to EEG tracings and the results of clinical investigations. Furthermore, all the included studies were carried out in specialized epilepsy centres on adult patients where refractory seizures or spells presenting a diagnostic problem are much more frequent than in community based population (referral bias and reduced generalizability of results).

5. Conclusions

In conclusion, a pooled analysis of data from the literature shows that urinary incontinence has no value either in the differential diagnostic between ES and NEEs considered as a whole or in the differential diagnosis between seizures and syncope/PNEEs. Systematic reviews with pooled analyses of data from the literature allow an increase in statistical power and an improvement in precision, representing an useful tool to determine the accuracy of a certain physical finding in the differential diagnosis between seizures and other paroxysmal events. Despite the useful information provided by an evidence-based approach to the evaluation of a physical sign, the diagnosis of epileptic seizure, syncope or other paroxysmal non-epileptic events requires careful integration of history, ictal signs and other clinical and investigational information, and should not be driven by any one clinical sign alone.

Conflict of interest statement

None.

Sources of funding statement

None.

Appendix A. Appendix

Search strategy

Urinary incontinence [MESH] and (epilepsy [MESH] OR epileps* OR epilept* OR seizur* OR seizures [MESH]) and (incontinence OR incontin*): 56 results.

Equations used to calculate accuracy measures of urinary incontinence

	Disease	No disease
Test positive	*a*	*b*
Test negative	*c*	*d*

nr1 = $a + b$nr2 = $c + d$nc1 = $a + c$nc2 = $b + dN = a + b + c + dz$ = 1.959964.

Sensitivity

Sensitivity = a/nc1.

Specificity

Specificity = d/nc2.

Positive Likelihood Ratio

LR+ = sensitivity/(1 − specificity)

Lower limit = $\exp(\ln((\text{nc2} \times a)/(\text{nc1} \times b)) - z\sqrt{((c/(a \times \text{nc1})) + (d/(b \times \text{nc2})))}$

Upper limit = $\exp(\ln((\text{nc2} \times a)/(\text{nc1} \times b)) + z\sqrt{((c/(a \times \text{nc1})) + (d/(b \times \text{nc2})))}$.

Negative Likelihood Ratio

LR + = (1 − sensitivity)/specificity

Lower limit = $\exp(\ln((\text{nc2} \times c)/(\text{nc1} \times d)) - z\sqrt{((a/(c \times \text{nc1})) + (b/(d \times \text{nc2})))}$

Upper limit = $\exp(\ln((\text{nc2} \times c)/(\text{nc1} \times d)) + z\sqrt{((a/(c \times \text{nc1})) + (b/(d \times \text{nc2})))}$.

References

1. Benbadis SR, Wolgamuth BR, Goren H, Brener S, Fouad-Tarazi F. Value of tongue biting in the diagnosis of seizures. *Archives of Internal Medicine* 1995;**155**:2346–9.
2. Brigo F, Nardone R, Bongiovanni LG. Value of tongue biting in the differential diagnosis between epileptic seizures and syncope. *Seizure* 2012;**21**:568–72.
3. Brigo F, Storti M, Lochner P, Tezzon F, Fiaschi A, Bongiovanni LG, et al. Tongue biting in epileptic seizures and psychogenic events. An evidence-based perspective. *Epilepsy & Behavior* 2012;**25**:251–5.
4. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1994;**271**:389–91.
5. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Statistics in Medicine* 1998;**17**:857–72.
6. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. *Journal of Clinical Epidemiology* 1991;**44**:763–70.
7. McGee SR. Diagnostic accuracy of physical findings. In: McGee SR, editor. *Evidence-based physical diagnosis.* Saunders Elsevier; 2007. p. 3–19.
8. Hoefnagels WA, Padberg GW, Overweg J, van der Velde EA, Roos RA. Transient loss of consciousness: the value of the history for distinguishing seizure from syncope. *Journal of Neurology* 1991;**238**:39–43.
9. Brown MC, Levin BE, Ramsay RE, Debra AK, Duchowny MS. Characteristics of patients with non-ES. *Journal of Epilepsy* 1991;**4**:225–9.
10. Peguero E, Abou-Khalil B, Fakhoury T, Mathews G. Self-injury and incontinence in psychogenic seizures. *Epilepsia* 1995;**36**:586–951.
11. Reuber M, Pukrop R, Mitchell AJ, Bauer J, Elger CE. Clinical significance of recurrent psychogenic nonepileptic seizure status. *Journal of Neurology* 2003;**250**:1355–62.
12. Oliva M, Pattison C, Carino J, Roten A, Matkovic Z, O'Brien TJ. The diagnostic value of oral lacerations and incontinence during convulsive "seizures". *Epilepsia* 2008;**49**:962–7.
13. Brigo F. Refining probability: a simple concept to be considered when interpreting interictal epileptiform discharges in EEG. *Journal of Clinical Neurophysiology* 2011;**28**:334.
14. Brigo F. An evidence-based approach to proper diagnostic use of the electroencephalogram for suspected seizures. *Epilepsy & Behavior* 2011;**21**:219–22.
15. Fagan TJ. Nomogram for Bayes theorem. *New England Journal of Medicine* 1975;**293**:257.