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Review

Value of tongue biting in the differential diagnosis between epileptic seizures and syncope

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ABSTRACT

Background: Tongue biting (TB) may occur both in epileptic seizures and in 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.
Aims: To undertake a systematic review and a meta-analysis of studies evaluating the prevalence of TB in patients with epileptic seizures and syncope, and to determine sensitivity, specificity and likelihood ratios (LR) of this physical finding.
Method: Studies comparing the prevalence of TB in epileptic seizures and syncope were systematically searched. Prevalence of TB was analyzed calculating odds ratio (OR) with 95% confidence intervals (CIs). Sensitivity, specificity, positive and negative likelihood ratio (pLR, nLR) of TB were determined for each study and for the pooled results.
Results: Two studies (75 epilepsy patients and 98 subjects with syncope) were included. There was a significantly higher prevalence of TB in patients with epileptic seizures (OR 12.26; 95% CI 3.99–37.69). Pooled accuracy measures of TB for the diagnosis of epileptic seizures were: sensitivity 33%, specificity 96%, pLR 8.167 (95% CI 2.969–22.461) and nLR 0.695 (95% CI 0.589–0.82).
Conclusions: A pooled analysis of data from the literature shows that TB has great value in the differential diagnosis between epileptic seizures and syncope. Given a certain pre-test probability of seizures, the presence of TB greatly increases the chance that the patient had an epileptic seizure. Systematic reviews with pooled analyses (meta-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 seizures and other paroxysmal events.

1. Introduction

Epileptic seizures are only rarely witnessed by physicians, so that the diagnosis is typically based on historical information supplemented by selected tests. A careful history, with a focus on details of the paroxysmal episode, is the single most important element in the diagnosis. When patients have limited or no recall of the event, such as following paroxysmal episodes of loss of consciousness, witnesses should be queried about details of the episode. However, even if witnesses can given an accurate description of the event, 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 epileptic seizures, syncope and psychogenic non-epileptic events. There are however other diagnoses which should be taken into account, including hypoglycemia, massive intracranial hemorrhage. An accurate neurological and general examination may provide additional information to support the initial diagnostic suspicion.

Tongue biting (TB) has long been considered useful for the clinical diagnosis of epileptic seizures, although it may occur both in patients with seizures and in subjects with syncope.[2] The diagnostic value of this physical finding is therefore debatable. Furthermore, a comprehensive search of the literature to determine the accuracy of this physical finding (with special regards to its positive likelihood ratio and to the sample size of each study) and its prevalence in epileptic seizures and syncope has not yet been performed.

In this study we therefore aimed to undertake a systematic review and a meta-analysis of studies evaluating the prevalence of TB in patients with seizure and syncope, and to determine the

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pooled sensitivity, specificity and likelihood ratios (LR) of this physical finding.

2. Methods

Our aim was to critically and systematically evaluate the literature to determine (a) the prevalence of TB in patients with epileptic seizures and syncope; (b) the sensitivity, specificity, positive LR (pLR) and negative LR (nLR) of this physical finding.

We included prospective and retrospective studies comparing the prevalence of TB between patients with epileptic seizures (all types) and patients with syncope. Only data on tongue lesions (not lacerations to the cheek, to the lip, or in other sites) were considered. No age, race or gender restrictions were applied. Studies could rely on historical reports of TB from patients, on direct examination of patients who presented to the emergency unit after a seizure, or on video-EEG monitoring evaluation.

Studies providing data on the TB prevalence without reporting the number of patients were excluded.

The MEDLINE (accessed by Pubmed; 1966 to April 2011) electronic database was searched using the following medical subject headings (MeSH): "Epilepsy", "Seizures" and "Tongue", as well as following free terms, combined in multiple search strategies with Boolean operators in order to find relevant articles: "tongue", "epileps*", "epilept*", "seizur*", "bit*", "biting", "bite" (see Appendix A). Furthermore, all references lists in identified trials were scrutinized for studies not indexed in the electronic database. 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 papers and articles already published were considered eligible for inclusion.

The methodological quality of each study was evaluated. Quality assessment of included studies focused on following criteria: (1) presence or absence of the target disorder (epileptic seizures/syncope) confirmed with a valid test ("gold" or reference diagnostic standard); (2) evaluation of the physical sign (TB) on an appropriate spectrum of patients; (3) application of both the physical finding being evaluated (TB) and the reference diagnostic standard to all patients; (4) comparison of the physical sign independent from and blind to the reference diagnostic standard.

Provided we thought it clinically appropriate, and no important clinical and methodological heterogeneity was found, we summarized results in a meta-analysis.

Prevalence of TB (dichotomous data) was analyzed by calculating odds ratio (OR) for each study, with the uncertainty in each trial being expressed using 95% confidence intervals (CIs). A weighted effect across studies was also calculated.

In case of sufficient data, we planned to undertake a subgroup analysis to assess the presence of oral lacerations involving the side of the tongue (lateral TB), presenting results on the same Forest plot to give an overall impression.

Homogeneity among study results was evaluated using a standard Chi squared test, combined with the I^2 statistics, and the hypothesis of homogeneity was rejected if the p value was less than 0.10. Prevalence was combined to obtain a summary estimate of value (and the corresponding CIs) using a random-effect model. Random-effects model is considered more conservative than a fixed-effect model, since it takes into account the variability between studies, thus leading to wider CIs.

The meta-analysis was undertaken with the Review Manager software developed by the Cochrane Collaboration (5.1). 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 B.[3–5]

Sensitivity measures the proportion of positives that are correctly identified, whereas specificity measures the proportion of negatives that are correctly identified. In the present review, sensitivity represents the proportion of patients with epileptic seizures who have TB, whereas specificity refers to the proportion of subjects without seizures (but with syncope) who lack TB.

The LR of a physical sign is defined as the proportion of patients with disease (epileptic seizure) who have a certain finding divided by the proportion of subjects without disease who also have the same finding.[5] A pLR refers to the presence of the physical sign, whereas a nLR refers to the absence of that physical sign. The interpretation of LRs is straightforward: (1) values greater than 1 increase the probability of disease, and the greater the LR, the more compelling the argument for disease; (2) values between 0 and 1 decrease the probability of disease, and the closer the LR is to zero, the more the finding argues against the diagnose of disease; (3) values equal zero have no diagnostic values, as they do not change pre-test probability.[5] A pLR describes therefore how probability changes when the finding is present, whereas nLR describes how probability changes when the finding is absent.

SPSS 16.0 was used to calculate accuracy measures. The random-effect model, which considers both within-study and between-study variance to calculate a pooled LR, was used to summarize the LRs from the included studies.[6]

3. Results

The search strategy described above yielded 72 results (71 MEDLINE, 1 in reference lists).

After reading the abstracts, eight studies were provisionally selected, but later excluded after reading the full text: six studies[7–12] did not provide enough data on TB occurring in patients with syncope to be included in the meta-analysis; one study[13] provided data on TB prevalence without reporting the number of patients; one study[14] did not specify the number of true/false positive/negative, thus preventing us to determine pooled accuracy measures. After reading the full text of the retrieved articles, 2 studies were therefore included.

3.1. Methodological quality assessment of included studies (Table 1)

Both included studies[15,16] had significant methodological limitations. None of the included studies specified which optimal reference standard was adopted to determine the presence or absence of syncope. In all included studies a clinical evaluation was performed by epileptologists (not by cardiologists) working in tertiary epilepsy centers and applied both to epilepsy and to syncope patients. In both included studies patients with syncope were evaluated by neurologists and not by cardiologist, thus possibly leading to inadequate or not uniform clinical/instrumental evaluations of these patients, who were investigated probably less accurately than epilepsy patients. Furthermore, in both included studies it was not specified whether all instrumental tests (e.g. 24 hours cardiac monitoring, tilt table) were performed in all patients with suspected syncope (partial verification bias). Based on the information provided, the spectrum of patients with epileptic seizures included predominantly[16] or selectively[15] patients with motor phenomena. Moreover, the spectrum of patients with syncope included in the study of Benbadis et al.[15] showed a predominance of cardiac arrhythmias, thus not being a representative sample of syncope which may be observed in daily practice (representative spectrum bias). In fact, the predominance of cardiac arrhythmias in this study probably reflects the presence of a population bias of a referral epilepsy center (i.e. the prevalence of cardiogenic syncope would be different in a different setting) and the inclusion criteria adopted. The choice of an appropriate

Table 1
Description of included studies.

Study	Group	Inclusion criteria	Exclusion criteria	Number of subjects, male/female	Age	Type of seizures/syncope	Diagnostic reference used	Type of study, information on TB
Hoefnagels et al.[16]	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 hour 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 hemorrhage. 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 hours 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 TB assessment was made independently and blinded to the diagnosis.
	S			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.		
Benbadis et al.[15]	ES	Bilateral motor (stiffening and/or shaking) phenomena, loss of consciousness, or both.	Typical complex partial seizures, with altered awareness but no loss of consciousness.	34,13/21	26 (range 3–57)	11 generalized epilepsy; 23 localization-related epilepsy.	Video-EEG with evaluation of both interictal and ictal data.	Prospective, direct documentation of oral lesions. Not reported whether TB assessment was made independently and blinded to the diagnosis.
	S	Bilateral motor (stiffening and/or shaking) phenomena, loss of consciousness, or both. At least one episode with complete loss of consciousness.	Patients with near syncope only.	45,24/21	63 (range 23–89)	28 cardiac arrhythmia (sick sinus syndrome, third-degree atrio-ventricular block, ventricular fibrillation or tachycardia); 6 vasovagal syncope; 11 postural hypotension.	Electrocardiography (routine and Holter monitoring), hemodynamic, tilt table, and autonomic reflex examinations.	Retrospective. All patients were questioned as to whether they had ever sustained a tongue injury with a faint, and, if the answer was yes, patients were further questioned and examined by the same observer for evidence of scars. TB assessment not independent/blinded to the diagnosis.

ES, epileptic seizures; S, syncope; SD, standard deviations; TB, tongue biting. –: not reported.

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

Study	Sensitivity	Specificity	pLR (95% CIs)	nLR (95% CIs)
Hoefnagels et al.[16]	41%	94%	7.325 (2.302–23.313)	0.62 (0.476–0.81)
Benbadis et al.[15]	24%	98%	10.588 (1.39–80.667)	0.782 (0.646–0.947)
Pooled results	33%	96%	8.167 (2.969–22.461)	0.695 (0.589–0.82)

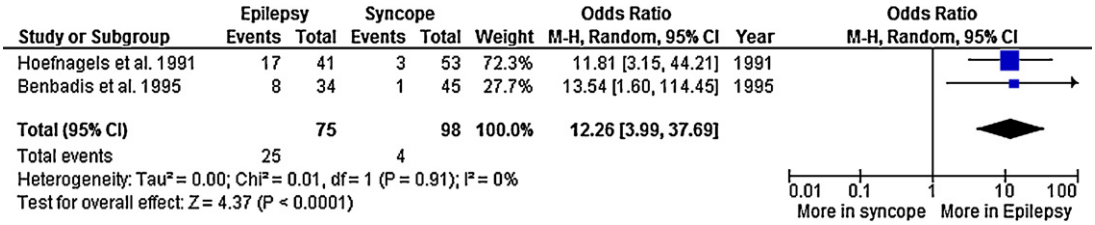

Fig. 1. Prevalence of TB.

spectrum of patients may have great influence on accuracy measures. For instance, when considering that TB occurs in patients with motor seizures, the adoption of less strict inclusion criteria (i.e. including also non-motor epileptic seizures) would decrease sensitivity of TB, without affecting specificity.

Only one study[16] performed the same diagnostic tests both in patients with epileptic seizures and in patients with syncope, whereas in the other included study, patients of the two groups underwent different diagnostic procedures.[15]

In all studies, it was not specified whether the presence of TB was evaluated independently from and blind to the reference diagnostic standard. One study was prospective,[16] whereas one study performed a prospective evaluation of epileptic patients, although data from patients with syncope were obtained retrospectively.[15] A retrospective evaluation of patients determining the presence of TB by history alone is likely to be less accurate than a prospective evaluation determining TB by means of physical examination.

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

3.2. Quantitative synthesis

3.2.1. Prevalence of TB (Fig. 1)

There were 2 studies with 173 participants (75 epilepsy patients and 98 patients with syncope). Significant statistical heterogeneity among trials was not detected. There was a statistically significant difference in the prevalence of TB between epilepsy and syncope group, with higher prevalence in epilepsy group (25/75 vs. 4/98 participants; OR 12.26; 95% CI 3.99–37.69).

3.2.2. Sensitivity, specificity, pLR and nLR of TB for the diagnosis of epileptic seizures

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

Pooled accuracy measures were: sensitivity 33%, specificity 96%, pLR 8.167 (95% CI 2.969–22.461) and nLR 0.695 (95% CI 0.589–0.82).

4. Discussion

The diagnosis of epileptic seizures 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, the diagnosis of seizures may be supported by clinical findings, such as TB. However, TB may occur also in patients with syncope, so that the diagnostic utility of this finding should be evaluated in the clinical context.

In this systematic review, we used systematic and explicit methods to identify, select and critically appraise studies, and to extract data, analyzing 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 and an improvement in precision, sometimes permitting to answer questions not posed by individual studies and to settle controversies arising from conflicting claims.

The meta-analysis showed a statistically significant difference in TB prevalence between epilepsy and syncope group, with higher prevalence in epilepsy. It is however noteworthy to consider that data were obtained by studies which predominantly16 or selectively15 included patients with motor phenomena.

Although in daily practice TB is a physical sign often used in the differential diagnosis of episodes characterized by paroxysmal loss of consciousness, it is rather surprising to consider that only two studies in the literature specifically aimed to assess the diagnostic validity of this sign. Any conclusion on such a topic should therefore be cautious because of the limited sample size of participants included in these two studies and because of the methodological limitations of these studies outlined in Section 3.1.

Pooled data on sensitivity and specificity obtained by the two included studies are consistent with data from a previous study[14] calculating these accuracy measures based on a retrospective evaluation of historical criteria in 102 patients with epilepsy and 437 patients with syncope (sensitivity of cut tongue was 45.1% and specificity 97.3%).

Pooled accuracy measures for TB showed a statistically significant pLR. If the probability of epileptic seizures 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,[17] the chance that the patient had an epileptic seizure appears to be greatly increased by the presence of TB (Fig. 2). The lack of data on the site of oral lacerations occurring in patients of one included study[16] prevented us from performing a subgroup analysis to assess this aspect. However the only patient with syncope and oral lacerations reported in the study conducted by Benbadis et al.[15] had a biting involving the tip of the tongue. Although definite evidence from the literature is still lacking, it has been suggested that a lateral TB tends to support a diagnosis of

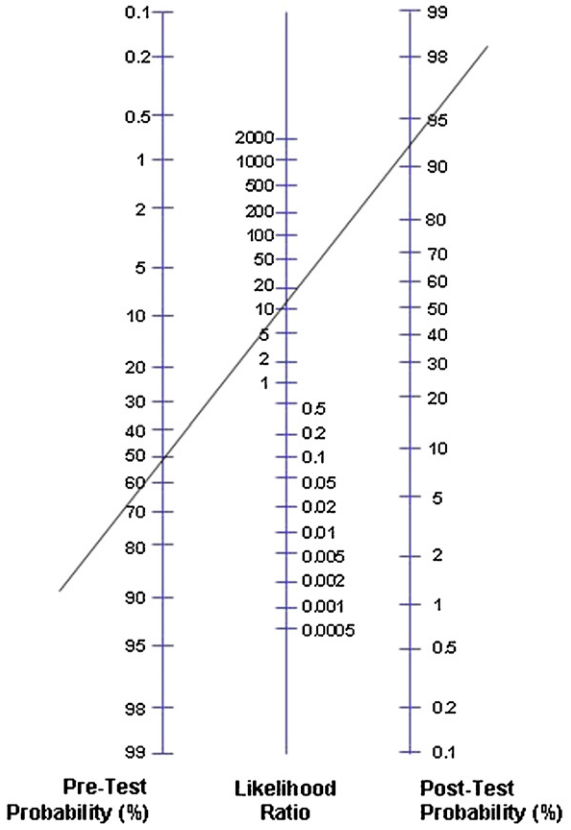

Fig. 2. The probability of epileptic seizures is estimated by means of a nomogram describing how pre-test probability relates to post-test probability given the LR for TB. When in doubt between the diagnosis of epileptic seizure and that of syncope, for instance given a pre-test probability of seizures of 50%, the presence of TB greatly increases the chance that the patient had an epileptic seizure (continuous line) (pLR = 8.167).

epileptic seizures, whereas anterior tongue lacerations have been considered to predominantly occur in syncope and psychogenic non-epileptic events.[15] Conversely, one study[2] has previously reported the presence of a lateral TB occurring during convulsive syncope, and however the limited amount of data on site of oral lacerations occurring during syncope available in the literature does not allow to draw any definite conclusion on such an aspect. Further studies aimed to specifically assess the site of TB occurring during syncope are therefore required.

5. Conclusions

In conclusion, a pooled analysis of data from the literature shows that TB has great value in the differential diagnosis between epileptic seizures and syncope. Systematic reviews with pooled analyses (meta-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 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 a careful integration of history, ictal signs and other clinical and investigational information, and should not be driven by any single clinical sign.

Conflict of interest statement: None.

Sources of funding statement: None.

Appendix A. Search strategy

(Tongue OR tongue [MESH]) and (epilepsy [MESH] OR epileps * OR epilept * OR seizur * OR seizures [MESH]) and (bit * OR biting OR bite).

Appendix B. Equations used to calculate accuracy measures of TB

	Epileptic seizure	Syncope (no seizure)
TB present	a	b
TB absent	c	d

nc1 = a + c
nc2 = b + d
z = 1.959964

Sensitivity
Sensitivity = a/nc1
Lower limit = $((2 \times a) + z^2 - z\sqrt{((4 \times a \times c/nc1) + z^2)})/((2 \times nc1) + (2 \times z^2))$
Upper limit = $((2 \times a) + z^2 + z\sqrt{((4 \times a \times c/nc1) + z^2)})/((2 \times nc1) + (2 \times z^2))$

Specificity
Specificity = d/nc2
Lower limit = $((2 \times d) + z^2 - z\sqrt{((4 \times d \times b/nc2) + z^2)})/((2 \times nc2) + (2 \times z^2))$
Upper limit = $((2 \times d) + z^2 + z\sqrt{((4 \times d \times b/nc2) + z^2)})/((2 \times nc2) + (2 \times z^2))$

Positive likelihood ratio*
LR+ = Sensitivity/(1 − Specificity)
Lower limit = $\exp(\ln((nc2 \times a)/(nc1 \times b)) - z\sqrt{((c/(a \times nc1)) + (d/(b \times nc2)))})$
Upper limit = $\exp(\ln((nc2 \times a)/(nc1 \times b)) + z\sqrt{((c/(a \times nc1)) + (d/(b \times nc2)))})$

Negative likelihood ratio*
LR+ = (1 − Sensitivity)/Specificity
Lower limit = $\exp(\ln((nc2 \times c)/(nc1 \times d)) - z\sqrt{((a/(c \times nc1)) + (b/(d \times nc2)))})$
Upper limit = $\exp(\ln((nc2 \times c)/(nc1 \times d)) + z\sqrt{((a/(c \times nc1)) + (b/(d \times nc2)))})$

* When calculating LR, if any cell of the 2 × 2 table contained the vale of zero, 0.5 was added to all cells, to avoid creating the unlikely LRs of 0 or infinity (McGee[5]).

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