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Value of patient-reported symptoms in the diagnosis of transient loss of consciousness

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Abstract:

Objectives: Epileptic seizures, syncope and psychogenic nonepileptic seizures (PNES) account for over 90% of presentations with Transient Loss of Consciousness (TLOC). The patient's history is crucial for the diagnosis, but the diagnostic value of individual semiological features is limited. This study explores the diagnostic potential of a comprehensive questionnaire focussing on TLOC-associated symptoms. **Methods:** 386 patients with proven epilepsy, 308 patients with proven PNES and 371 patients with proven syncope were approached by post to recruit 100 patients in each diagnostic group. Symptoms were self-reported on an 86-item questionnaire (the Paroxysmal Event Profile, PEP) using a five-point Likert scale ("always" to "never"). Data were subjected to Exploratory Factor Analysis (EFA) followed by Confirmatory factor analysis (CFA). Factors were used to differentiate between diagnoses by pairwise and multinomial regression.

Results: Patients with PNES reported more and more frequent TLOC-associated symptoms than those with epilepsy or syncope (p<0.001). EFA/CFA identified a five-factor structure based on 74/86 questionnaire items with loadings ≥ 0.4 . Pair-wise logistic regression analysis correctly classified 91% of patients with epilepsy versus those with syncope, 94% of those with PNES versus those with syncope, and 77% of those with epilepsy versus those with epilepsy versus those with epilepsy versus those with PNES. Multinomial logistic regression analysis yielded a similar pattern.

Conclusions: Clusters of self-reported TLOC symptoms can be used to direct patients to appropriate investigation and treatment pathways for syncope on the one hand and seizures on the other, although additional information is required for a reliable distinction, especially between epilepsy and PNES.

Value of patient-reported symptoms in the differential diagnosis of transient loss of consciousness

Introduction

Transient Loss of Consciousness (TLOC) is the second most common neurological emergency ¹. Three conditions account for over 90% of presentations: epilepsy and psychogenic nonepileptic seizures (PNES) and syncope ^{2,3}. Accurate distinction between these conditions is crucial because treatment choice depends on it. Unfortunately, misdiagnosis rates of over 25% have been reported in different primary and secondary care settings⁴⁻⁶. The gold standard test in this situation would be the synchronous recording of a typical event by video, heart rhythm by ECG, and electrical brain activity by EEG. However, in many patients, the observation of spontaneous episodes of TLOC is impractical or impossible.

Previous research suggests that there is no single demographic, clinical or semiological feature, which distinguishes clearly between epilepsy, syncope or PNES ^{4,7}. In routine clinical practice, the diagnosis is usually based on a combination of facts derived from the patient's history and witness accounts (if available). The diagnosis also takes account of interictal investigations like blood pressure recordings, ECG, EEG and brain CT or MRI, although these investigations are of limited utility ⁸⁻ ¹¹. However, in the absence of a clear pre-test probability of one specific cause of TLOC, interictal test abnormalities may be misinterpreted, especially by non-experts ⁵, ^{6,12}. The misdiagnosis of PNES is particularly common. In fact, almost all patients with this disorder initially receive a diagnosis of epilepsy or syncope ^{13, 14}. The mean latency between manifestation and diagnosis of PNES is four to seven years, putting patients at risk of inappropriate emergency treatments and even death ^{13, 15, 16}.

For these reasons recent epilepsy management guidelines emphasise the need for an early expert assessment¹⁷. Unfortunately, access to experts is limited and even experts currently lack evidence-based tools that would allow them to express the level of certainty with which they have made their initial clinical diagnosis: an accurate determination of a post-test probability of a particular diagnosis would require a clear understanding of its pre-test probability ¹⁸.

The present study determines whether a comprehensive profile of patients' TLOC experiences can contribute to the differentiation between all three common causes of this clinical phenomenon and explores whether such a questionnaire can provide a pre-test probability adding value to the interpretation of interictal investigations.

Materials & Methods

Patients: Epilepsy & PNES groups – Patients with epilepsy or PNES supported by video-EEG recordings of typical seizures involving TLOC were identified from clinical databases of the Department of Clinical Neurophysiology at the Royal Hallamshire Hospital in Sheffield and the National Hospital of Neurology and Neurosurgery in London, UK.

Syncope group – Patients with a diagnosis of recurrent syncope supported by pathophysiological evidence (typical warning symptoms or complete TLOC associated with typical heart rate or blood pressure changes during a tilt-table test / presyncopal or syncopal symptoms associated with explanatory heart rate or rhythm changes during ECG monitoring) were identified from the centres above and the database of the Falls and Syncope Service based at Newcastle upon Tyne, UK.

Patients with one of the causes of TLOC were approached by post until 100 in each diagnostic group had returned completed questionnaires. The clinical diagnoses of all patients were confirmed by each patients' consultant neurologist / physician. All patients were ≥ 16 years at the time of the study.

Sample size - We recruited a total sample of n=300 (100 per group) to allow us to conduct factor analyses across all participants as well as to test for moderate differences (effect size >=0.40) between groups with at least 80% power ¹⁹.

Paroxysmal Event Profile (PEP) - The 86-item PEP included questions previously shown to differentiate between tonic clonic seizures and syncope ^{20, 21}. It also included questions thought by experts, amongst whom earlier versions of this questionnaire were circulated, potentially to differentiate between epilepsy and PNES. Additional items were based on ideas derived from metaphor analytic studies suggesting that patients with epilepsy perceive their episodes of TLOC as opponents with independent agency whereas those with PNES experience their TLOC as a space or place they themselves go through ^{22, 23}. The PEP also contained questions about dissociation (based on the Dissociative Experience Scale Taxon) ²⁴ and about

symptoms of panic listed in the DSM-IV-TR ²⁵. Responses were invited on a fivepoint Likert scale ("always"/"frequently"/"sometimes"/"rarely"/"never"). In addition to the 86 items focusing on TLOC manifestations, respondents were asked to answer seven questions about demographic and clinical features (see PEP questionnaire for details).

Study procedure - PEP questionnaires were sent out by post with a free return envelope and an information sheet stating that the return of the completed questionnaire would be interpreted as consent. Patients were incentivised to return the questionnaires by the offer of participation in a prize draw for a digital radio (value £60, \$80).

Statistical analysis – Overall mean symptom scores for each subject were calculated for each diagnostic group and compared using ANOVA. Frequencies of reporting extremes, ("never" or "always" responses) were tabulated and compared between diagnostic groups using Chi² statistics.

An Exploratory Factor Analysis (EFA) of the PEP items was conducted using geomin oblique rotation. Items with factor loadings ≥0.4 were retained. In a Confirmatory Factor Analysis (CFA) the factor structure suggested by the EFA was subjected to Goodness of Fit statistics, including Root Mean Square Error Approximation (RMSEA), Comparative Fit Index (CFI) and Tucker Lewis Index (TLI). RMSEA < 0.06, CFI > 0.90 and TLI >0.90 were predetermined as standards for good model fitting.

Mean factor scores were compared across the three diagnostic groups and differences tested using one-way ANOVA. To assess the ability of all of the factors simultaneously to discriminate participants by diagnostic groups, pair-wise and multinomial logistic regression analyses were used with all five factor scores as continuous predictors. Separate models including models using only one factor score at a time were also produced. In addition to regression models based entirely on self-reported TLOC symptom factors, we report regression models combining TLOC symptom factors with additional 'patient demographic / clinical information' (self-reported data on gender, number of episodes of TLOC in last year, lifetime number of hospitalisations, and whether or not there had been any admissions to intensive care for the treatment of TLOC or whether there was a family history of TLOC). All clinical variables were included as categorical predictors (as in Table 1). Age and age at onset were not included in models including patients with syncope because syncope patients were predominantly recruited in a healthcare setting attracting older adults.

All factor analyses were conducted in Mplus Version 7.0. Logistic regression was performed in SAS Version 9.3 for Windows. Two-sided p-values ≤ 0.05 were considered statistically significant. The ANOVA on 86 items was controlled for multiple testing (i.e. significance was determined at 0.05/86 = 0.00058).

Standard protocol approvals, registrations, and patient consent - Ethical approval for this study was granted by the Northern and Yorkshire Multi-Centre Research Ethics Committee. Patients were informed that their return of the completed PEP questionnaire would be considered as consent to the analysis and publication of the data provided.

Results

Respondents –386 patients with epilepsy, 308 with PNES and 371 with syncope were approached until 100 patients had been recruited in each group, see table.

Descriptive findings - The mean item scores for each PEP question by the three diagnostic groups are presented in Figure 1. As indicated by the darker shading of the PNES column in figure 1, patients in this group reported more frequent symptoms overall (mean score 2.4 where 1 is "never" and 5 is "always") than those with epilepsy (mean score 2.0) or syncope (mean score 1.8, differences: PNES versus epilepsy p<0.0001, epilepsy versus syncope p=0.007). PNES were also associated with a wider range of symptoms reflected by the lower number of white squares in the PNES column in figure 1 and by the lower mean percentage of "never" replies in the PNES group (46.1%) than the epilepsy (60.3%) or syncope (73.4%) groups (differences PNES versus epilepsy p<0.0001, epilepsy versus syncope p<0.0001). As indicated by the significantly lower percentage of "extreme" (i.e. "never" plus "always"), PNES (59.4%) emerged as a less stereotyped phenomenon than epilepsy (70.4%) or syncope (82.9%, differences PNES versus epilepsy p<0.0001, epilepsy versus syncope p<0.0001, epilepsy versus syncope p<0.0001, epilepsy versus syncope for syncope (70.4%) or syncope (82.9%, differences PNES versus epilepsy p<0.0001, epilepsy versus syncope p<0.0001, epilepsy versus syncope p<0.0001).

Responses to 57 out of 76 items differed significantly between the three diagnostic groups in an ANOVA ($p \le 0.0005$). Only 10 items P2, P5, P8, P10, P20, P26, P34, P74, P80 and P84 did not differentiate between the three groups even at the more liberal 0.05 level.

Latent factor analysis – EFA models with one to six factors were tested due to there being six eigenvalues greater than 1. Models with four to six factors all had a good model fit (RMSEA ≤ 0.05 and CFI/TLI ≥ 0.90), but the five-factor model was favored for its better interpretability. Of the 86 items, 74 had factor loadings ≥ 0.4 . Seven loaded on two, the remaining items on one latent factor. The five-factor structure, with the selected 74 items, was tested by CFA. The fit indices of CFA model were CFI=0.93, TLI =0.92 and REMSA=0.04.

Based on our semantic interpretation, the five latent factors were named "feeling overpowered ", "sensory experience", "mind/body/world disconnection", "catastrophic experience" and "amnesia" (see Table 2 for more details). The mean factor scores from the CFA analysis across the epilepsy (E), PNES (P) and syncope (S) groups are shown in Figure 2. The factors "feeling overpowered", "mind/body/world disconnection" and "catastrophic experience" were significantly different between all three groups (p<.001), while "amnesia", only differentiated syncope , and "Sensory experience" only epilepsy from the other two diagnostic groups (p<.001) (see table 3 for more details)..

Differential diagnostic value of latent factors - Initial pair-wise logistic regression established the discriminating power of the factors between each pair of the three possible clinical diagnoses (table 4). The combination of symptom-based factor scores and basic 'patient demographic / clinical information' (excluding age and age at onset) correctly classified more patients than the symptom-based data alone. In each regression, the factor scores (based on patients' self-reported seizure experiences)

contributed more to the differential diagnosis than 'patient demographic / clinical information'.

Multinomial logistic regression analysis revealed a similar pattern to the analyses described above: 91 out of 100 (91%) syncope diagnoses could be predicted correctly. Correct classification rates were lower for epilepsy and PNES: 63 out of 96 (66%) epilepsy patients and 74 out of 95 (78%) PNES patients were classified correctly, and most of the confounding was between these two diagnostic categories as well (the PNES and epilepsy groups contained fewer than 100 patients because some demographic / clinical details had not been provided by a small number of participants).

Discussion

Our study demonstrates that a comprehensive self-report tool focussing on TLOCassociated symptoms can differentiate with high accuracy between syncope and the other two common causes of TLOC and slightly less well between PNES and epilepsy. This finding is of considerable clinical importance because it shows that self-reported symptom profiles can help direct patients to the most appropriate specialist services and provide a numeric pre-test probability enhancing the diagnostic value of interictal investigations.

Whilst to date, no diagnostic self-report tool designed to aid the differentiation between all three common causes of TLOC has been tested, a 118-item questionnaire used in 671 patients achieved a correct differentiation between recurrent generalized tonic clonic seizures or syncope in 94% of cases ²¹. However, patients with loss of

awareness without collapse or those with PNES were excluded from this study. In another study, a 29-item patient questionnaire was used in combination with a 6item witness questionnaire to identify patients who ultimately received an expert diagnosis of "epileptic seizure" from a group of 94 patients with TLOC. Unfortunately, a logistic regression model based on four items (age, sweating before the event, tongue biting and witnessed rapid orientation after the event) worked least well in uncertain cases ²⁰.

Another project (excluding those with probable syncope) used a 209-item questionnaire in patients referred for video-EEG with possible diagnoses of epilepsy or PNES. This self-report tool categorised patients correctly with a sensitivity and specificity of 85% ²⁶. Whilst only a small proportion of questions used in this study asked about subjective seizure symptoms, other studies suggest that the subjective experiences and patients' accounts of PNES differ from those of epileptic seizures ^{23, 27-32}.

It is a particular strength of our study that the clinical diagnoses of all participants had been proven by the recording of typical TLOC episodes during appropriate physiological monitoring. Previous studies aiming to validate diagnostic questionnaires have often used much lower diagnostic standards, for instance the working diagnosis after a certain period of follow-up ^{20, 21}, the opinion of an experienced clinician ³³, or the diagnosis recorded in medical registers ^{34, 35}. Given how important the patient's history is for the diagnosis, validation studies not involving objective confirmation by the recording of a typical episode of TLOC are at risk of demonstrating a match between a clinician's history-taking efforts and a

history taken by questionnaire rather than a match between the actual diagnosis and the diagnostic questionnaire result. Having said this, the fact that we deliberately chose patients with medical "gold standard" diagnoses means that our findings were based on a relatively chronic patient population. Now that there is clear "proof-ofconcept" that a symptom-based questionnaire can contribute to the differential diagnosis of TLOC, we can use the results of our study to identify the most highly discriminating questions and develop a shorter questionnaire specifically for use in clinical settings where patients initially present with TLOC.

In our study patients with PNES reported more different and frequent TLOCassociated symptoms than those with epilepsy or syncope. These observations are consistent with a previous study which demonstrated a greater range of subjective ictal experiences in PNES than epilepsy ²⁸. They could simply reflect the tendency of patients with PNES to report higher rates of physical symptoms generally – as demonstrated by studies using general somatisation measures ^{36, 37}. However, impairment of consciousness associated with PNES patients may also be less profound than that associated with the other two disorders ^{38, 39}, Thirdly, TLOC caused by PNES may be a less stereotyped experience. This interpretation would be supported by the lower ratio of "extreme" versus "middling" responses seen in this group.

Our study demonstrates that self-reported symptom profiles made a greater contribution to the diagnostic models than the available demographic and clinical facts, although the addition of these facts improved the accuracy of the diagnostic models. The models did not differentiate equally well between all three causes of

TLOC: our self-report tool accurately categorised over 90% of patients with either epilepsy or syncope. Similar levels of diagnostic separation were achieved in the distinction of patients with PNES from those with syncope. However, even when information derived from symptom reports was combined with demographic/clinical information, our detailed questionnaire only classified 77% of patients accurately when we attempted to distinguish between epilepsy and PNES (82% with the additional consideration of age at onset). The high levels of correct differentiation between syncope and epilepsy are in keeping with the results of previous studies ^{20, 21}. However, in contrast to the previous studies, our study includes a well-characterised group of patients with PNES, a condition as common in neurology clinics as syncope ^{2, 3}. This means that our findings are applicable to a wider range of patients including those with partial or absence seizures involving TLOC, not only those with generalised tonic clonic seizures, on which the largest similar previous study focused ²¹.

Whilst responses to 57 of the 86 items in the PEP questionnaire differed between the diagnostic groups, questions asking about symptoms of disconnection and patients' tendency to catastrophize made the greatest contribution to the three-way differentiation. Responses to these questions suggested that PNES more than epileptic seizures and both of these types of TLOC more than syncope involve ictal experiences similar to those which characterise dissociative or anxiety disorders.

Our study has a number of limitations. Given that we were keen to base our study on patients with "gold standard" diagnoses, our findings are derived from patients who presented to specialist centres. The fact that the participants in all diagnostic groups

studied were predominantly female meant that the groups were well-matched for gender but also suggests that males may have been underrepresented, at least in the epilepsy group. Our findings may also have been affected by the response rate: whilst a rate of around 30% may be all that is achievable in a postal study of this kind, there may have been significant differences between patients who participated in this study and those who did not. The relatively high number of episodes of TLOC and long duration of TLOC disorders is likely to have enabled respondents to answer questions about their symptoms particularly well. However, the preferential inclusion of patients with relatively chronic disorders means that our findings should be replicated in other settings before they are generalised more widely. We can also not rule out that patients' symptom reporting was influenced by them being aware of their diagnosis. For instance, patients with PNES may have been encouraged by doctors to reflect on the presence of dissociative or anxiety symptoms. Last but not least, the differential diagnostic value of self-reported subjective symptoms could be greater if they had been combined with information only obtainable from other sources, for instance from witnesses. For instance, it may have been helpful to know whether collapses were atonic or involved shaking.

Despite these limitations, our study clearly demonstrates that the different pathophysiological mechanisms causing TLOC in epilepsy, PNES and syncope are associated with different TLOC experiences. Self-reported TLOC manifestations differentiate well between patients with syncope and those with seizures. However, the distinction of epileptic from non-epileptic seizures was less secure. Self-report tools based on TLOC manifestations can therefore be used to guide patients to relevant medical investigation and treatment pathways (eg. cardiology for syncope,

neurology for seizures) and they can help to quantify the post-test probability of

particular diagnoses.

Figure legends:

Figure 1:

Short title: Range and frequency of self-reported TLOC-symptoms in patients with epilepsy, syncope and PNES

Legend: Graphic representation of the respondents' mean answers to the 86 questions posed in the PEP illustrating the relative diagnostic value of individual items. Mean answers are indicated for each group by the light blue line. The shade of the background colour also indicates the mean response (with dark shades reflecting less frequent experiences and light shades more frequent experiences).

Figure 2:

Short title: TLOC-symptoms profiles in epilepsy, syncope and PNES

Legend: Symptom profiles based on five latent factors characterising the subjective patient experience of the three common causes of TLOC (means and standard error bars).

Table 1: Overview of demographic and clinical characteristics of the three respondent

 groups (continuous variables are shown as means (standard deviation) and discrete

 variables as counts).

		Epilepsy (N=100)	PNES (N=100)	Syncope (N=100)	p-value
Age (years)	-	35.4 (14.5)	41.6 (13.5)	53.5 (21.6)	< 0.0001 [°]
Age at onset (years)	-	12.2 (11.4)	26.4 (15.2)	39.4 (25.0)	< 0.0001 °
Duration (years)	-	23.2 (13.6)	15.0 (15.9)	14.1 (16.8)	< 0.0001 ^d
Gender	Female Male	71 29	71 29	77 23	0.54 ^e
TLOC in last year ^a	None Up to 5 Up to 50 More than 50	17 18 31 31	10 7 40 43	21 50 25 4	< 0.0001 °
Hospitalisation* ^b	Never Once up to 5 More than 5	32 17 19 31	23 16 29 27	82 7 10 1	< 0.0001 ^f
Intensive Care*	No Yes	84 16	84 16	99 1	$0.0005^{\rm f}$
Family History	No Yes	72 28	71 29	76 24	0.70 °

* Self-reported lifetime number of hospitalisations with TLOC

a: Number of TLOC unknown in 3 patients with epilepsy.

b: Hospitalisation information for 1 patients with epilepsy and 5 with PNES is missing.

c: All three pair-wise comparisons had p-value <0.05.

d: All except PNES vs. syncope comparisons had p-values <0.05.

e: None of three pair-wise comparisons had p-value <0.05.

f: All except PNES vs. epilepsy comparisons had p-values <0.05.

Table 2: Five latent factors - sample questions contributing to the different factors.

	Number of	Item numbers		
Factor name	items loading	loading onto	Typical items	
	onto factors	factor		
Feeling overpowered	10	p2, p8-p13, p17 p18, p65	p9. My attacks well up inside me.p17. Just before my attacks I feel anxious onervous.	
Sensory experience	11	p1, p3, p4, p16 p19-p22, p24- p26	P24. In my attacks my vision goes dim or dark.P25. In my attacks sounds are distorted	
Amnesia	11	p1, p34, p45, p76, p77, p80- p83, p85, p86	P82. After my attacks I feel very confused.P83. Afterwards I have no idea that I have had an attack.	
Mind/body/world disconnection	27	p11, p14, p15, p26-p29, p32, p36, p38-p40, p42-p44, p46- p56, p60	P43. During an attack, I feel as if otherpeople, objects, and the world are not real.P50. During my attacks I feel as if I'm not aperson.P51. During my attacks I feel as if I'm notin the living world.	
Catastrophic experience	22	p21, p23, p31, p33, p35, p37, p41, p55, p56, p58, p61-p64, p66-p70, p73, p78, p81	 P41. I am aware of shaking uncontrollably during an attack. P69. My attacks are painful - like a hammer blow. P70. My attacks feel like a knife through the head. 	

Table 3. ANOVA demonstrating the differentiating potential of individual factor

scores between the three possible causes of TLOC.

	Diagnosis	Diagnosis	Factor difference estimate	P-value
	Е	Р	-0.05546	0.0033
Feeling overpowered	Е	S	0.06974	0.0002
	Р	S	0.1252	<.0001
	E	Р	-0.2203	<.0001
Sensory experience	Е	S	-0.2299	<.0001
	Р	S	-0.00968	0.8465
	E	Р	-0.01703	0.4965
Amnesia	Е	S	0.2383	<.0001
	Р	S	0.2553	<.0001
	E	Р	-0.3737	<.0001
Mind/body/world disconnection	Е	S	0.5341	<.0001
	Р	S	0.9078	<.0001
	E	Р	-0.5506	<.0001
Catastrophic experience	E	S	0.4202	<.0001
	Р	S	0.9709	<.0001

Table 4. Binary Logistic Regression demonstrating differentiating potential of factor

 scores or demographic/clinical patient information or both combined.

Outcomes	Covariates	N *	Sensitivity	Specificity	Total Accuracy (%)
PNES	Factor Scores	200	0.78	0.72	75
vs	Patient Information	191	0.74	0.46	60
Epilepsy (ref)	Combined	191	0.80	0.74	77
G	Factor Scores	200	0.87	0.83	85
Syncope vs Epilepsy (ref)	Patient Information	196	0.88	0.68	78
	Combined	196	0.92	0.91	91
PNES Vs Syncope (ref)	Factor Scores	200	0.93	0.87	90
	Patient Information	195	0.85	0.85	85
	Combined	195	0.95	0.93	94

*: A total of 9 subjects had some missing demographic or clinical infromation

listed in table 3, and were not included in these analyses.

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Figure 1: Graphic representation of mean responses to all PEP items in the three diagnostic groups. Items are ranked in order of self-reported frequency (most frequent symptoms at the top).





