Tilt-induced vasovagal syncope and psychogenic pseudosyncope

Overlapping clinical entities

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ABSTRACT

Objective: To describe the combination of tilt-induced vasovagal syncope (VVS) and psychogenic pseudosyncope (PPS) and aid its clinical recognition.

Methods: We identified people with tilt-induced VVS/PPS from 2 tertiary syncope referral centers. For each case, 3 controls with tilt-induced VVS were selected at random from the same center. Clinical characteristics were compared between both groups adjusting for multiple comparisons.

Results: Of 1,164 tilt-table tests, 23 (2%) resulted in VVS/PPS; these 23 cases were compared with 69 VVS controls. VVS and PPS coincided more often than chance would predict: 2% vs 0.6%, $p < 0.001$. Typical VVS prodromes and triggers were reported in all people with VVS/PPS and in controls with VVS. Attack frequency was significantly higher in the VVS/PPS (2 per month, range 0.1–60) than in the VVS group (0.25 per month, range 0.02–4; $p < 0.001$). Delayed recovery of consciousness was more frequently reported in the VVS/PPS group (likelihood ratio [+LR] 8.14, 95% confidence interval [CI] 3.94–16.84), as well as episodes without prodromes (+LR 5.57, 95% CI 2.53–12.26), atypical triggers (+LR 5.00, 95% CI 2.04–12.24), eye closure (+LR 3.75, 95% CI 1.68–8.35), and apparent loss of consciousness >1 minute (+LR 2.86, 95% CI 1.98–4.13).

Conclusions: VVS/PPS presents with a complex phenotype. High attack frequency, delayed recovery of consciousness, apparent loss of consciousness >1 minute, ictal eye closure, atypical triggers, and the absence of prodromes may serve as indicators that PPS coincides with VVS.

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GLOSSARY

AED = antiepileptic drug; **BP** = blood pressure; **CI** = confidence interval; **HR** = heart rate; **LR** = likelihood ratio; **LUMC** = Leiden University Medical Centre; **PNES** = psychogenic epileptic seizure; **PPS** = psychogenic pseudosyncope; **SEIN** = Stichting Epilepsie Instellingen Nederland; **TLOC** = transient loss of consciousness; **VVS** = vasovagal syncope.

Transient loss of consciousness (TLOC) is a frequent presentation, with vasovagal syncope (VVS) as the most common cause.[1] Establishing the cause of TLOC can be difficult, especially when individuals present with 2 conditions simultaneously. The most reliable diagnosis of TLOC is obtained if appropriate pathophysiologic data are recorded during an attack recognized as typical by the individual. Blood pressure (BP), heart rate (HR), or both are low during VVS, but tend to be high during psychogenic pseudosyncope (PPS).[2] We previously noted that PPS either preceded or followed VVS in 12 out of 800 tilt-table tests, a pattern we label here as VVS/PPS.[2] This parallels the situation of psychogenic epileptic seizures (PNESs), which are also found more often in people with epileptic seizures.[3–5] Our previous study demonstrated that individuals with PPS had longer periods of apparent TLOC and were more likely to have their eyes closed during apparent TLOC than those with VVS.[2] A sudden head drop or sliding down the tilt table was more frequent in individuals with PPS, whereas those with VVS were more likely to exhibit jerking movements. People with VVS/PPS may present with a mixture of the 2 sets of features, but this has not yet been described. Early recognition of VVS/PPS is important to avoid excessive testing. VVS features are probably better known than those of PPS. This

Editorial, page 2000

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might cause PPS elements in VVS/PPS to be missed, so that VVS/PPS would be mistaken for VVS. We therefore compared the clinical characteristics of patients with VVS/PPS with those of VVS only, searching for features that distinguish the 2 groups.

METHODS **Patients.** We selected people with tilt-induced VVS/PPS at 2 tertiary referral centers for syncope: Leiden University Medical Centre (LUMC, 800 tilt-table tests, April 2006 to April 2012)[2] and Stichting Epilepsie Instellingen Nederland (SEIN Heemstede, 364 tilt-table tests, January 2009 to June 2014). All individuals were clinically examined and all tilt-table tests inspected by neurologists with a special interest in TLOC and syncope (LUMC: J.G.v.D., SEIN: R.D.T.). In both centers, tilt-table testing is carried out using ECG, continuous BP monitoring, and continuous video-EEG monitoring. Initial evaluation, data acquisition, and tilt-table test procedures at both centers are uniform, as J.G.v.D. and R.D.T. have been collaborating closely for approximately 15 years. The criteria for tilt-induced VVS were described previously and consisted of video data compatible with loss of consciousness, circulatory changes comprising an abrupt BP decrease with an accelerating rate of drop with or without bradycardia/asystole, and EEG changes consisting of a slow or a slow-flat-slow pattern.[3] PPS was also defined based on previously described criteria: apparent TLOC during tilt-table testing without EEG changes and without decreases in HR or BP.[2] If VVS was preceded or followed by PPS, the episode was labeled as demonstrating VVS/PPS. For each case of VVS/PPS, we randomly selected 3 controls with tilt-induced VVS from the same center and time period. In both the VVS and VVS/PPS groups, the tilt-induced events had to be recognized by the individual or a relative, present during the test, as typical of the individual's spontaneous episodes. Participants were excluded if another condition was present that could explain their apparent TLOC, i.e., epilepsy, cardiac syncope, orthostatic hypotension (cases and controls), or PPS (controls only).

Standard protocol approvals, registrations, and patient consents. This study was approved by the ethics committee of the LUMC. As all data were acquired during routine clinical care, no informed consent was required at either site.

Tilt-table test protocol and data collection. Tilt-table testing was used to provoke episodes of apparent TLOC and conducted according to a modified Italian protocol as described previously.[4] The information in case notes had been obtained during an interview prior to tilt-table testing. The following data were extracted from patient files: sex, age at testing, age at onset of apparent TLOC (childhood onset was set at 6 years of age and teenage onset at 15 years), time from first apparent TLOC to final diagnosis, previous diagnostic workup including number of consulted specialists prior to evaluation, use of an implantable loop recorder, past use of antiepileptic drugs (AEDs), average number of episodes in the year before presentation, and the occurrence of apparent TLOC >1 minute. For each individual, we recorded whether classical VVS triggers (i.e., pain, emotion, standing up, prolonged standing/sitting, cessation of exercise, recent meals) and typical VVS prodromes (i.e., lightheadedness, blurred vision, poor concentration, nausea, sweating, and pallor) were present. In addition, features atypical of VVS were recorded. These factors included episodes with atypical triggers (exercise, or supine position in the absence of a concomitant trigger such as venipuncture), episodes without prodromes, eye closure during apparent TLOC, shivering or heavy breathing during apparent TLOC, inability to prevent any episode of apparent TLOC by sitting or lying down, and delayed recovery of consciousness. Recovery of consciousness was considered delayed if any of the following features was recorded: (1) failure to regain consciousness in the supine position; (2) recovery of consciousness requiring tactile stimulation; (3) attempts by bystanders to resuscitate the patient; or (4) a prolonged period of confusion after the event.

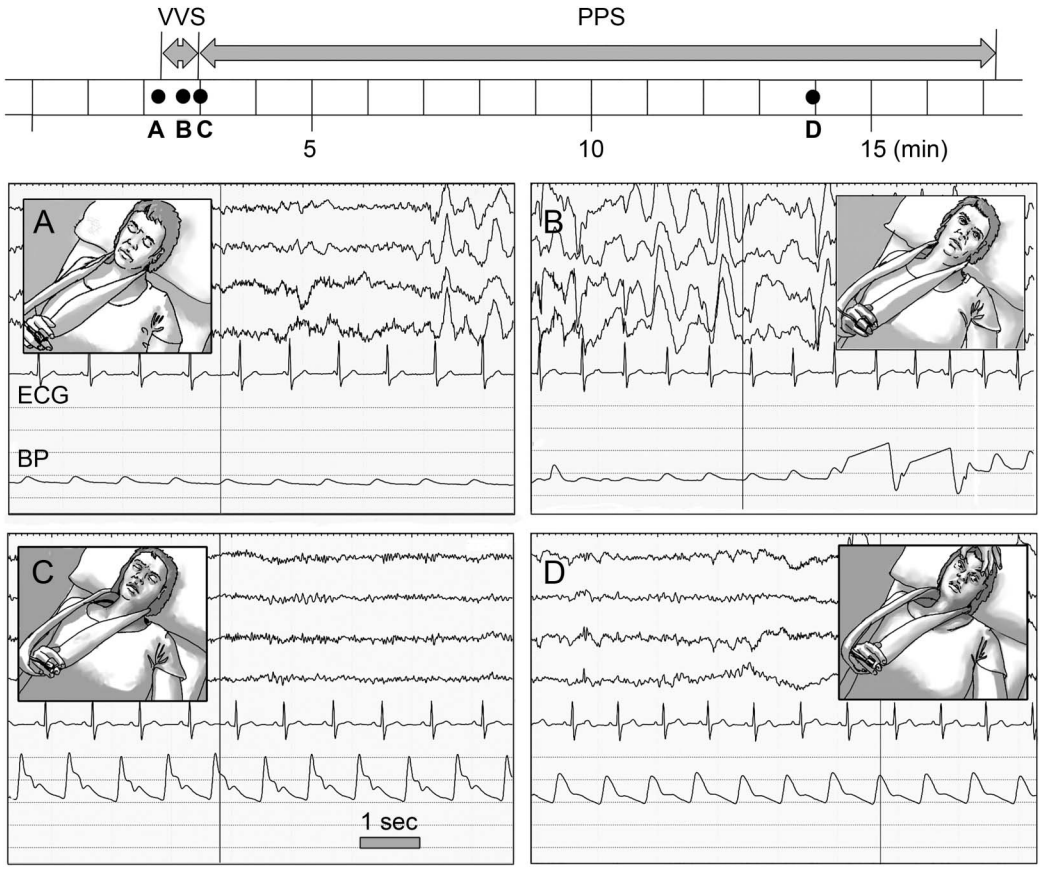
In view of the retrospective evaluation, we made the assumption that all features atypical of VVS were absent if not recorded. Routine assessment at both centers includes a 45- to 60-minute narrative-based interview of all previous apparent TLOC events by neurologists with expertise in VVS and PPS, so it is likely that atypical features would have been noted and recorded. All clinical data were reviewed by an experienced neurologist with a special interest in syncope (R.D.T.).

Statistics. A χ^2 goodness-of-fit test was used to determine whether VVS and PPS coincided more frequently than based on chance alone. Clinical characteristics were described and differences between groups were analyzed using χ^2 statistics (Pearson or Fisher exact test where appropriate) for categorical and the Mann-Whitney U test for continuous data. p Values of <0.05 were considered to be significant. Bonferroni adjustment for multiple comparisons was made. We made 16 comparisons, thus resulting in a significance threshold $\alpha = 0.05/16 = 0.0031$. Those features in the history with a dichotomous outcome that remained significant after Bonferroni adjustment were expressed as likelihood ratio (+LR) (sensitivity/1 − specificity) with 95% confidence intervals (CIs). All analyses were performed with SPSS (version 17.0 for Windows; Chicago, IL).

RESULTS Of 1,164 tilt-table tests, 205 (18%) were labelled as presyncope, 143 (12%) as VVS, 51 (5%) as PPS, and 23 (2%) as mixed VVS/PPS. VVS and PPS would be expected to co-occur in only 7 tilt-table tests, considering the proportions of VVS and PPS in our sample: $0.12 \times 0.05 \times 1{,}164$. VVS and PPS, therefore, coincided more frequently than chance would predict: 23 vs 7 ($p < 0.001$). In 19 of the 23 cases (83%), PPS immediately followed VVS despite normalization of HR, BP, and EEG. In the remaining 4 cases (17%), PPS either occurred immediately (n = 1) or several minutes (n = 3) before the onset of VVS.

Medication use in cases and controls is detailed in table e-1 on the Neurology® Web site at Neurology.org. An illustrative case is presented in figure. The frequency of certain features was compared between the 23 people with VVS/PPS and the 69 with VVS (table 1). Typical VVS prodromes and triggers were reported in all VVS/PPS cases and VVS controls. People with VVS/PPS tended to be younger than those with VVS and a female preponderance was noted (96% vs 65%, $p < 0.004$: not significant after Bonferroni adjustment). Classical triggers and typical prodromes of VVS were reported by all people with VVS/PPS and VVS controls. Those with VVS/PPS had a higher attack frequency than controls (2 per month vs 0.25 per month, $p < 0.001$). Delayed

Figure Example of consecutive VVS and PPS



Data from 4 time points during a tilt-table test (A–D) are shown. The time bar above the panels displays the temporal sequence of these events; point 0 occurred approximately 20 minutes after tilt-up. The time scale within each panel is shown in panel C. To improve clarity, only 4 EEG leads are shown. Video images were drawn to enhance visibility and protect privacy: facial features were altered. At point A, blood pressure (BP) is already low; the ECG shows disappearance of P-waves and AV-node escape beats. The EEG develops pronounced slowing; at this point, the patient is lying with the eyes voluntarily closed. Tilting down commences. Point B shows pronounced slow EEG activity, ventricular escape beats, and low BP (barring 2 artefacts). The patient's facial expression is vacant, with the eyes wide open and staring ahead. At point C, EEG, ECG, and BP have just normalized, but the patient is still immobile with eyes closed, and has not yet responded. Point D occurs within the next 15 minutes, during which the patient remains immobile and nonresponsive with eyes closed, although the EEG is normal. At this point, the examiner opens the patient's eyes, which deviate away from the examiner. This does not result in a verbal response. PPS = psychogenic pseudosyncope; VVS = vasovagal syncope.

recovery of consciousness was more frequently reported in the VVS/PPS group (+LR 8.14, 95% CI 3.94–16.84), as well as apparent TLOC >1 minute (+LR 2.86, 95% CI 1.98–4.13). Apparent TLOC >1 minute often coincided with delayed recovery of consciousness ($\chi 2[1]$, $p < 0.001$). Other significant differences in the VVS/PPS group when compared to the VVS group were a higher proportion of episodes without prodromes (LR 5.57, 95% CI 2.53–12.26), atypical triggers (LR 5.00, 95% CI 2.04–12.24), and eye closure (LR 3.75, 95% CI 1.68–8.35). People with VVS/PPS more frequently expressed an inability to prevent episodes by getting seated/supine than those with VVS, but this variable did not reach significance after correction for multiple comparisons. Indicators of diagnostic delay or misdiagnosis such as the time to diagnosis, the number of specialists consulted, use of AEDs, or loop recorder implantation did not differ between groups.

DISCUSSION PPS and VVS coincide more frequently than chance would predict. We studied a cases series with tilt-proven combined attacks of VVS and PPS to identify features that help distinguish VVS/PPS from pure VVS.

We found that VVS/PPS presents with a complex phenotype. All cases reported typical VVS triggers and prodromes, but also atypical features. High attack frequency, delayed recovery of consciousness, the absence of prodromes, atypical triggers, eye closure, and apparent TLOC >1 minute may suggest that PPS coincides with VVS. A limitation of our study is its retrospective nature. However, the tilt-test criteria on which the group allocation was based were

Table 1 Clinical characteristics of participants with tilt-induced VVS/PPS and those with tilt-induced VVS

	VVS/PPS (n = 23)	VVS (n = 69)	*p* Value	+LR (95% CIs)
Female	22 (96)	45 (65)	0.004	—
Age, y	26 (16–59)	41 (10–77)	0.022	—
Age at onset, y[a]	16 (6–58)	18.5 (3–66)	0.327	—
Time to diagnosis, y[a]	6 (0.3–41)	6 (0.1–70)	0.564	—
No. of consulted specialists	2 (1–4)	2 (1–5)	0.597	—
Previous implantation of loop recorder	2 (9)	3 (4)	0.596	—
Past use of AEDs	3 (13)	4 (6)	0.361	—
Inability to prevent apparent TLOC	21 (91)	41 (59)	0.005	—
Shivering during apparent TLOC	3 (13)	6 (9)	0.686	—
Heavy breathing during apparent TLOC	3 (13)	3 (4)	0.163	—
Episode frequency (number per month)[b]	2.0 (0.1–60)[c]	0.25 (0.02–4)[c]	<0.001[c]	—
Delayed recovery of consciousness	19 (83)[c]	7 (10)[c]	<0.001[c]	8.14 (3.94–16.84)[c]
Report of episodes without prodromes	13 (57)[c]	7 (10)[c]	<0.001[c]	5.57 (2.53–12.26)[c]
Episodes with atypical triggers	10 (43)[c]	6 (9)[c]	<0.001[c]	5.00 (2.04–12.24)[c]
Eye closure during apparent TLOC	10 (43)[c]	8 (12)[c]	0.002[c]	3.75 (1.68–8.35)[c]
Apparent TLOC >1 minute	21 (91)[c]	22 (32)[c]	<0.001[c]	2.86 (1.98–4.13)[c]

Abbreviations: AED = antiepileptic drug; CI = confidence interval; LR = likelihood ratio; PPS = psychogenic pseudosyncope; TLOC = transient loss of consciousness; VVS = vasovagal syncope.
Dichotomous data are expressed as n (%) and continuous data as median (range). The Bonferroni-corrected significance level is $\alpha = 0.05/16 = 0.0031$. Typical VVS prodromes and triggers were reported in all VVS/PPS cases and VVS controls.
[a] This value was unknown in 2 cases and 5 controls.
[b] This value was unknown in 1 case and 18 controls.
[c] Significant association.

unequivocal and rigorously applied. The frequency of reported clinical characteristics may have been affected by the fact that the treating neurologists (J.G.v.D. and R.D.T.) preferentially recorded signs and symptoms deemed clinically relevant at the time of consultation. The presence or absence of each characteristic was, therefore, not systematically documented. Our relatively modest number of cases may have introduced a sampling effect. The characteristics of both components of the VVS/PPS pattern, however, correspond well with those of separate VVS and PPS populations in previous studies, suggesting that our sample may be representative.[2,3] Another possible limitation is not related to the study design: eyewitness accounts always need to be interpreted with caution. In a previous study, students asked to recall clinical features of a video-recorded episode did so with only 60% accuracy.[6] The estimation of event duration in particular may be affected by recall bias. This may explain why delayed recovery of consciousness, which consisted of more reliable clinical features, such as a failure to regain consciousness when supine, was a more specific marker of VVS/PPS than apparent TLOC >1 minute (table 1). We therefore favor the use of these telltale indicators of delayed recovery rather than estimates of the event duration. The most distinguishing features of the history were recorded in charts prior to tilt-table testing, i.e., blinded to our gold standard. These features conform well to our previous video-analysis of pure PPS,[2] suggesting that our conclusions are valid.

We identified several clinical characteristics that may suggest the coincidence of VVS and PPS. It is rare to diagnose any cause of apparent TLOC based on a single feature in the history.[1,5] For example, prolonged duration of apparent TLOC may be suggestive of VVS/PPS, but cannot rule out other causes of apparent TLOC such as isolated PPS.[2] In fact, even VVS may be prolonged under specific circumstances: a persistent trigger (instrumentation),[7] when participants are (inadvertently) kept upright,[8] when VVS results in concussion or a tonic-clonic seizure (in children),[9] or when VVS is followed by sleep (children).[10] The diagnosis, therefore, should take as many features of as many attacks as possible into account. Indeed, history taking of people with VVS/PPS often suggests separate features for VVS and PPS, which can be disentangled based on knowledge of semiology of VVS[7] and PPS.[2,11] Our study may give the impression that VVS/PPS is a rare condition, as it only occurred in 2% of all tilt-table tests in 2 tertiary referral centers. We only selected cases, however, where both conditions were documented during a single tilt-table test. Other tilt-table results such as isolated VVS, isolated PPS, or no TLOC do not necessarily exclude the coincidence of VVS/PPS in everyday life. Our

stringent inclusion criterion may therefore have caused an underestimation of the prevalence of VVS/PPS. In our experience, VVS/PPS is a common scenario among those with chronic and apparent refractory syncope. We did not find evidence that the time to diagnosis or the number of consulted specialists distinguished the groups. The rates of use of AEDs or implanted loop recorders were also similar in participants with VVS/PPS and those with VVS. This may suggest that the more severe clinical expression of VVS/PPS (in terms of attack frequency and duration of apparent TLOC) had not prompted an aggressive diagnostic approach. Those with VVS had also been referred to tertiary care, presumably because of perceived complexity.[11] In PNESs it has been well-established that a timely and accurate diagnosis may help to reduce the burden for individuals and the health care system.[12–16]

The double nature of VVS/PPS may warrant multiple therapeutic approaches. Our clinical impression is that when PPS attacks dominate the clinical picture, this should be the main focus of attention.[11,17,18] When VVS is the dominant issue, however, it may be sufficient to give instructions on physical countermaneuvers and lifestyle advice.[19–21] This advice provides individuals with control over the situation, reducing anxiety, and might therefore be beneficial for both vasovagal and psychogenic episodes. However, the efficacy of any treatment in PPS is unknown, so these issues need appropriate study.[18,22]

AUTHOR CONTRIBUTIONS

The study was conceptualized and designed by H.B., R.J.L., and R.D.T. Data were collected by H.B., R.J.L., and R.D.T. Data were analyzed and interpreted by H.B., R.J.L., J.G.v.D., and R.D.T. The article was drafted by H.B., R.J.L., J.G.v.D., and R.D.T. All authors approved the submitted version. R.D.T. is the guarantor.

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