Syncope causes transient focal neurological symptoms

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Summary

Aims: The prevalence of focal neurology (FN) as a consequence of syncope is unknown. The aim of the study was to determine its prevalence, risk factors and short-term consequences.

Methods: A consecutive sample of syncope-unit attendees during a 9-month period had detailed diagnostic syncope evaluation as per European Cardiac Society guidelines coupled with assessment for FN present during syncope/pre-syncope by screening questionnaire, follow-up interview and neuroimaging (1.5T magnetic resonance imaging [MRI]). All participants were followed up for 24 months. Risk factors for FN were identified by comparing FN cases with syncope controls without FN (3:1 ratio).

Results: Five-hundred and forty consecutively attended for investigation of syncope (n = 401) and pre-syncope (n = 139). Thirty-one (5.7%) had FN events during hypotensive symptoms, mean age 49 years (19–85). The majority of FN cases had vasovagal syncope (VVS); 22 (71%), whereas eight had OH (25.8%) and one (3.2%) had cardiac arrhythmia. Median duration of FN was 15 min (IQR: 34.5). MRI in 28 (90%) was normal and in 3, old cerebral infarction was evident. Risk factors for FN/syncope were frequent syncope (P = 0.008), childhood syncope (P < 0.0005) and delayed diastolic recovery during active stand (P = 0.02). During 24-month follow-up and targeted intervention, no patients developed recurrence of FN.

Conclusion: One in 20 patients with syncope/pre-syncope have co-extant FN, which during 24-month follow-up, does not progress to a persistent deficit (>24 h). Awareness of co-occurrence of FN and syncope is important as stroke misdiagnosis results in aggressive anti-hypertensive management and future events may ensue.

Introduction

It is necessary to distinguish syncope from a transient ischemic attack or a stroke as misdiagnosis may lead to counter productive interventions. Syncope is one of the most common presentations to medical services. Its management is challenging because patients present to many specialists such as internists, cardiologists, neurologists, emergency physicians, and geriatricians and there is a wide variation in practice and applications of guidelines for its evaluation and management.

Diagnosis of syncope is predominantly dependent on characteristics of the event elicited during history taking. Syncope guidelines were developed to address challenges with diagnosis and syncope management units evolved to ensure appropriate delivery of the guideline recommendations.1

Syncope is defined as a transient loss of consciousness due to global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery.1 Co-occurrence of focal neurology (FN) is highly unlikely. For example, the European Society of Cardiology (ESC) Taskforce for Syncope guidelines state that ‘a TIA concerns a focal deficit without loss of consciousness, and syncope the opposite’.1 Similarly, the
guideline recommendation from the American Heart Association/American Stroke Association Stroke Council states that a stroke or a TIA results from focal rather than global insult, which precludes syncope. Yet, a number of recent case reports suggest a causal association between syncope and focal neurological events.

Because syncope is due to cerebral hypoperfusion, it is biologically plausible that haemodynamic-related, focal neurological events could occur during syncope. Misdiagnosing syncope-induced FN as a stroke or a transient ischemic episode exposes patients to more aggressive blood pressure (BP) lowering therapies, which could exacerbate syncopal episodes and further neurological sequelae, underpinning the importance of this clinical distinction.

The aim of this study was to determine the prevalence of FN in consecutive patients with syncope, the outcome for these patients after treatment of attributable causes of syncope and the risk factors for FN in syncopal patients.

Methods

Patients

Consecutive patients with syncope or pre-syncope who presented to a dedicated unit in a large teaching hospital were recruited during a 9-month period between January and September 2012 and followed up for median 24 months to June 2014. In addition to a detailed history of syncope and pre-syncope, all were prospectively questioned about co-occurrence of FN during events. Additional information was prospectively collated regarding details of FN during episodes including description and frequency of events.

Assessments

All patients underwent comprehensive cardiovascular assessment, which included detailed syncope and pre-syncope history, including childhood events (i.e. were you a frequent fainter as a child), medication history, physical examination, surface electrocardiogram and orthostatic BP recordings. A 10-year cardiovascular risk profile (Framingham-derived calculation based on age, body mass index, baseline systolic BP (SBP), BP medication, smoking status and the presence of diabetes) was used to explore an association between vascular burden and the occurrence of FN as this might suggest an ischemic source. Other investigations included active stand, carotid sinus massage, echocardiogram, ambulatory heart rate (HR) and BP monitoring, cardiac imaging and electrophysiological study in accordance with the current ESC Guidelines.

Active stand

Phasic measurement of HR and BP (digital plethysmography; Finapres Pro, Philips Medical) was recorded in all patients during 3 min standing after 10 min supine rest. Baseline BP was defined as average BP 60–30 s before standing. Changes from baseline in SBP, diastolic BP (DBP) and HR were used in analysis.

Diagnoses

The consensus definition of orthostatic hypotension (OH) was used, which is defined as a decrease in SBP of >20 mmHg or DBP >10 mmHg, in the 3 min after standing. Vasovagal syncope (VVS) was diagnosed when a history suggestive of VVS was coupled with symptom reproduction during head-up tilt testing. Cardiac syncope was attributed to patients who exhibited bradyarrhythmia, heart block, sick sinus syndrome, atrial or ventricular tachycardia sufficient to potentiate loss of consciousness, as detected by external or internal loop recorders.

The Questionnaire for Verifying Stroke-Free Status was used to screen for FN during syncope/pre syncope (Figure 1). The somatiform symptoms questionnaire, Patient Health Questionnaire-15 (PHQ-15), was utilized to correct for bias caused by the inclusion of somatiform cases. Patients rate how ‘bothered’ they are by 15 common symptoms including back pain, dizziness, chest pain, palpitations and insomnia. Higher scores correlate with an increased likelihood of the presence of a somatiform disorder. It is well validated and correlates with sick leave yet does not correlate with the presence of co-morbid disease. The community prevalence of somatiform disorder approximates to 6% based on a recent meta-analysis of seven observational studies. We excluded 6% of cases and controls with highest scores. A stroke and syncope physician determined co-occurrence and exclusion of other causes of FN (Figure 1).

Risk factors for FN during syncope

To ascertain risk factors for FN syncope, three controls per case were identified. Controls, selected from the initial sample of 509 patients (540 less the 31 controls), did not have FN and were matched for gender, age within 4 years and syncope diagnosis. Syncope history, medications, comorbidities and orthostatic BP and HR responses were compared for cases and controls.
Neuroimaging

FN cases also underwent a 1.5 T Magnetic resonance imaging (MRI) brain or computed tomography (CT) brain (if MRI was contraindicated) to exclude underlying brain pathology. Standard sequence protocol consisted of an axial T2-weighted turbo spin echo (TR 4639, TE 96 ms, FOV 200 mm, 4 mm slices), an axial fluid attenuation inversion recovery sequence (TR 1100, TE 140, FOV 200 mm, 4 mm slices) and axial diffusion weighted imaging sequence (TR 3343, TE 100, b values 0 and 1000). MRI scans were reviewed for evidence of infarction and white matter disease (WMD) as per standardized criteria. Location and severity of WMD were estimated on T2 and FLAIR scans using the Fazekas scale. Periventricular and deep white matter hyperintensities were rated by

Figure 1. Screening and identification of patients with FN and syncope/pre-syncope. CI, contraindication.
increasing severity for a total of 10 locations in the brain. Patients were dichotomized into a mild WMD group (scores 0–7) and a severe WMD group (score > 7).\textsuperscript{18}

**Intervention and follow-up**

Standard treatment protocols were applied for syncope diagnoses. These included avoidance of triggers, lifestyle modification, increase in fluid and salt intake, physical counter manoeuvres, reduction or withdrawal of culprit medication, prescription of midodrine and/or fludrocortisone, cardiac pacing, etc.\textsuperscript{1,19} FN cases were followed up for mean 24 months after intervention to ascertain whether recurrent FN occurred.

**Controls**

Controls were derived simultaneously from the syncope unit. Controls differed from cases in that they denied any history of FN during hypotensive symptoms. They were matched to cases according to age (within 5 years), gender and hypotensive disorder in a 3:1 ratio.

**Statistical analysis**

Based on pilot data (90 syncope-unit attendees), the sample-derived estimate of FN was 7.5%, thus screening 410 patients should identify 30 cases. It was estimated that three to one case–control design had 90% power to detect a 30% difference in migraine prevalence (ID-migraine), somatoform symptoms scores (PHQ15) and 10-year cardiovascular risk profile (Framingham-derived calculator). Descriptive statistics, chi-square test, Fisher’s exact test and Student’s \( t \) test were performed to analyse the relationship between the variables. Multivariate regression was used to further explore differences between the cases and controls. A hierarchical strategy was used where covariates were entered into the model in a series of planned steps. The data were entered into a Microsoft Excel Workbook and analysed in Stata 12.

**Results**

Of 540 patients, 401 reported syncope and 139 pre-syncope, mean age 56.4 years (range 14–92) and 65% were female (\( n = 351 \)). Median number of syncope episodes was 2 (IQR: 4) in previous year.

Of 72 patients with symptoms suggestive of FN, 32 were excluded because FN occurred independently of hypotensive symptoms (eight of these had symptoms both during and independent of hypotensive episodes) or because FN symptoms were attributed to epilepsy (5) or migraine (2). A further two cases were excluded because of high somatoform scores (PHQ15) (Figure 1).

In all, 31 patients had FN during hypotensive symptoms (Table 1). Thus, 5.7% of all syncope-unit attendees describe FN during hypotensive symptoms. The mean age in cases was 49 years (range: 19–84 years), 22 (71%) were female, 22 patients had VVS (71%), 8 (25.8%) OH and one (3.2%) cardiac syncope (bradyarrhythmia).

Syncope burden was high in FN cases. The mean number of syncopal episodes in the preceding year was eight (95% confidence interval [CI]: 2.2–13.8). Twenty cases (64.5%) also reported frequent syncope in childhood.

The majority of neurological events were motor (24, 77.4%) lasting for a median of 15 min (IQR: 34; one episode lasted > 24 h). The details of their FN are outlined in Table 2.

In 20 FN patients, acute neurological symptoms had been previously investigated, 8 (40%) were attributed to a TIA or stroke, in 9 (45%) no diagnosis was established, while in only 3 was FN attributed to hypotension. The remaining eleven (35%) FN patients failed to report FN symptoms to a health care professional.

**Neuroimaging**

All had brain MRI bar 2 patients (head CT scan) in whom MRI was contra indicated.\textsuperscript{20} Twenty-eight (90.3%) cases exhibited no acute or old infarct or other focal intracranial lesion. Two cases exhibited an old infarct in the corresponding hemisphere, and one case exhibited an old infarct in the non-corresponding hemisphere. Twelve cases had no WMD, 11 had mild WMD (scores 1–7) and 8 had severe WMD (score > 7). The details of their WMD scores are outlined in Table 3.

**Management**

All patients were given conservative advice including increased fluid and salt intake, physical counter manoeuvres, reduction or withdrawal of culprit medication, prescription of vasopressors or cardiac pacing.\textsuperscript{1}

**Follow-up**

After an average of 24-month follow-up (range: 21–29 months), no patient experienced further FN during pre-syncope/syncope or independent of syncope.

**Case–control comparison**

Comparisons between cases (FN patients) and syncope controls are presented in Table 1. Cases were
much more likely to report childhood syncope (64.5% vs. 18.3%, \( P < 0.0005 \)) and more frequent syncope in the prior year, \( P = 0.008 \). Somatoform scores were similar in cases and in controls \( (P = 0.47) \), as was prevalence of migraine, hypertension, depression and epilepsy. Vascular burden was equal in both groups, based on Framingham-derived 10-year cardiovascular risk, \( P = 0.93 \), Table 1.

After controlling for anti-hypertensive medication and co-morbid disease, cases were 7.7 times more likely to report childhood syncope (95% CI: 2.9–20.2, \( P < 0.0005 \) and 1.5 times more likely to...
report more frequent syncope in the prior year (95% CI: 1.1–2.16), P = 0.02.

Analysis of beat-to-beat BP response during active stand revealed that DBP recovered more slowly in cases. At 30 s post-stand, the recovery delay was significant even after confounding for medication and baseline BP (73 mmHg versus 80.1 mmHg, P = 0.02). SBP and HR responses were not significantly different, Figure 2.

Discussion

Of consecutive patients with syncope, 5.7% describe FN events associated with hypotensive symptoms. These findings differ from the European syncope guidelines, which state ‘For all practical purposes a TIA concerns a focal deficit without LOC, and syncope the opposite’\(^1\), while the American Academy of Neurologists state that a TIA is caused by ‘focal brain…ischemia’ and not global hypoperfusion.\(^2,21\)

Consequently, the presence of FN frequently and understandably leads to a diagnosis of stroke. A stroke/TIA had been diagnosed in 40% of our cases. Crucially, further lowering BP may aggravate the underlying condition, which is VVS in 71% (n = 22) and OH in 25.8% (n = 8).

Clinically, it is important to note that the presentation belies a benign condition, in 71% syncope was due to VVS (diagnosed through comprehensive syncope assessment, including head-up tilt) and 25.8% due to OH. Moreover, no acute infarct was identified in any case, and on follow-up, no patient developed an acute infarct. In fact, neuroimaging was reported as ‘normal’ in 28 cases (90.3%), with the exception of chronic WMD. Finally, no patient exhibited a persistent neurological deficit after a mean 24-month follow-up.

Although neuroimaging was largely negative, 17 scans were conducted in the non-acute period (>2 weeks); this is a limitation of the study. Acute infarcts may have resolved by time of scans. However, infarcts typically evolve into permanently identifiable lesions in up to 90% of cases.\(^{22}\) Thus it is unlikely acute infarction explains these events, especially given that 17 patients (54.8%) experienced more than one event. Moreover, vascular risk profile was similar in cases and controls (Framingham 10-year cardiovascular risk).

Fortunately, these patients exhibit some identifiable characteristics. Lifetime syncope burden is high. All report a history of pre-syncope or syncope, most report childhood syncope (64%) and frequent syncope (mean eight times in the previous year).

### Table 2 Focal neurological symptoms

<table>
<thead>
<tr>
<th>Description</th>
<th>N = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region affected, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>One limb involved</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>One side involved (2 limbs)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Facial droop</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Unilateral visual loss</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td><strong>Predominant function affected, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>24 (77.4)</td>
</tr>
<tr>
<td>Sensory</td>
<td>6 (19.3)</td>
</tr>
<tr>
<td>Vision</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td><strong>Associated hypotensive event, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Pre-syncope</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td><strong>Side affected, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>Right</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td>Alternating sides</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td><strong>Categorization, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>TIA</td>
<td>30 (96.8)</td>
</tr>
<tr>
<td>Median duration of FN, min (IQR)</td>
<td>15 (34.5)</td>
</tr>
<tr>
<td><strong>Events</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with &gt;1 such event, n (%)</td>
<td>17 (54.8)</td>
</tr>
<tr>
<td>Number of focal neurological events (SD)</td>
<td>27 (30.9)</td>
</tr>
<tr>
<td>Duration of focal neurological events, years (SD)</td>
<td>2.5 (2)</td>
</tr>
</tbody>
</table>

SD, standard deviation. Mean value unless otherwise stated.

### Table 3 Neuroimaging results

<table>
<thead>
<tr>
<th>Description</th>
<th>N = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No defect seen</strong></td>
<td>28 (90.3)</td>
</tr>
<tr>
<td><strong>Defect seen</strong></td>
<td>3 (9.7)</td>
</tr>
<tr>
<td><strong>Defect in corresponding hemisphere</strong></td>
<td>2</td>
</tr>
<tr>
<td>Gliosis temporal region</td>
<td>1</td>
</tr>
<tr>
<td>Left occipital infarct</td>
<td>1</td>
</tr>
<tr>
<td><strong>Defect non-corresponding hemisphere</strong></td>
<td>1</td>
</tr>
<tr>
<td>Right PCA infarct with right-sided weakness</td>
<td>1</td>
</tr>
<tr>
<td><strong>WMD score (Fazekas)</strong></td>
<td></td>
</tr>
<tr>
<td>WMD 0–7, n (%)</td>
<td>23 (74.2)</td>
</tr>
<tr>
<td>WMD &gt;7, n (%)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>WMD score in the corresponding hemisphere (SD)</td>
<td>1.83 (2.21)</td>
</tr>
<tr>
<td>WMD score in the non-corresponding hemisphere (SD)</td>
<td>1.9 (2.23)</td>
</tr>
</tbody>
</table>

SD, standard deviation. Mean value unless otherwise stated. PCA=posterior cerebral artery.
FN is usually brief, lasting a median of 15min and associated with either syncope or with pre-syncope. FN abnormalities are usually limb paresis, often in one limb or the face.

We can only hypothesize as to the underlying cause for their FN. Migraine is probably not responsible, as migraine prevalence (ID-migraine questionnaire) was equal in both groups. Somatoform disorders can present with neurological symptoms and this study was self-report based. However, a validated somatoform questionnaire (PHQ15) was included and FN patients had similar somatoform scores to that of controls.

FN syncope may be associated with impaired cerebral autoregulation, given that, on active stand, cases exhibited delayed diastolic recovery. \( P = 0.02 \) at 30 s.\(^{23,24} \) It is conceivable that a more severe phenotype of syncope coupled with impaired autoregulation causes severe tissue insult that culminates in focal neuronal hibernation but not ischemia. Global hypoperfusion correlates with localized tissue injury in cardiac arrest patients, who often develop unilateral cerebral infarction.\(^{25} \) Evidence from quantitative EEG monitoring with head-up tilt suggests that, in the immediate pre-syncopal period, patients exhibit a slow wave activity which is predominantly left lateralized, suggesting a heterogeneous autoregulatory response to global hypoperfusion.\(^{26} \)

Alternatively ischemia of central autonomic centres could explain our findings.\(^{27-29} \) However, in all cases, regular hypotensive symptoms predated FN and in no case did neuroimaging reveal acute ischemia.

Intra-cranial stenosis with hypotension could explain our findings. Although intracranial imaging was not routinely carried out on all patients, all cases were of Caucasian ethnicity and the prevalence of intracranial disease among such a population is only 1%.\(^{20} \)

WMD could also explain the observed results but we did not find an increase in WMD on the side that corresponded to neurological symptoms. However, the study was underpowered to demonstrate this effect. Certainly, there is a recognized association between syncope and WMD, so a larger sample may have uncovered this association.\(^{30} \)

Regardless of the pathophysiology, the important message is a clinical one. These patients should receive a diagnosis of syncope with FN and require appropriate management of the syncope cause. A misdiagnosis of TIA episodes could lead to more aggressive BP lowering strategies and further exacerbation of syncope.

**Ethics**

Ethical approval was obtained in advance from the Joint Hospitals Research Ethics Committee 2009/12/05.

**Funding**

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**Conflict of interest:** None declared.

**References**


