

## SHORT REPORT

# Multidisciplinary approach for diagnosing syncope: a retrospective study on 521 outpatients

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**Objectives:** To describe causes of syncope in outpatients in whom structural heart disease was ruled out as a cause, and to analyse the role of a multidisciplinary approach in a syncope unit for the diagnosis of patients with syncope of unknown origin.

**Methods:** Cardiovascular autonomic nervous system (ANS) function was evaluated extensively in 521 outpatients by careful history, physical examination including orthostatic blood pressure measurement and standard ECG, and tilt testing.

**Results:** Causes of syncope remained unknown in 29.2% of cases. ANS dysfunction was found in 58.6% of those presenting with either neurally mediated syncope (53.6%) or chronic autonomic failure (5%); 3.8% of the patients suffered from syncope of cardiogenic origin (2.5%) or non-neurogenic hypotension (1.3%), and 8.4% had loss of consciousness of non-syncopal origin. Loss of consciousness was confirmed as being related to seizures in under 30% of patients initially diagnosed as having epilepsy.

**Conclusions:** Neurally mediated syncope represents the commonest type of syncope. ANS evaluation including tilt testing should be considered as preliminary screening in patients with syncope in the absence of definite heart abnormalities. Neurologists should consider syncope from ANS failure as a comorbid factor in patients with seizures where the clinical characteristics are not straightforward.

Causes of syncope remain unknown in about half of all patients.<sup>1</sup> Questions persist on the diagnosis and management of syncope.<sup>2–4</sup> We retrospectively evaluated causes of syncope in 521 outpatients who had previously been investigated for heart disease. Physicians from our neurocardiovascular investigation unit interact continuously and closely with referring specialists. As a result, patients benefit from a multidisciplinary approach until the final diagnosis is reached and their clinical and therapeutic follow up is fully planned.

## METHODS

### Patients

Between June 1994 and February 2001, 655 consecutive patients with a diagnosis of syncope of unknown origin were referred to the service for the study of cardiovascular autonomic regulation at the Cardiovascular Pathophysiology Unit, University of Rome “La Sapienza”. Of these, 521 (79.5%) were considered for the retrospective analysis presented in this paper. These patients had two or more episodes of syncope or at least three episodes of presyncope during the 12 months preceding the first visit to our centre, and did not have heart disease or syncope related ECG changes.

Neurologists referred nearly 70% of the patients. Emergency room physicians, general practitioners, internal medicine specialists, and cardiologists had previously referred these patients to the neurologists.

Three types of patient were ultimately referred to our centre by neurologists:

- patients whose diagnosis of epilepsy had not been definitely ruled out;
- patients with syncope-like clinical findings with no clear evidence of epilepsy, neurodegenerative, or cerebrovascular disease;
- patients with syncope-like clinical findings associated with epilepsy.

The diagnosis of epilepsy was based upon clinical history, neurological examination, magnetic resonance imaging, standard electroencephalography (EEG) repeated three times over six months, 24 hour EEG, and sleep deprivation EEG. Patients with other certain diagnosis of any central nervous system (CNS) disorder other than epilepsy were excluded.

Emergency room physicians and general practitioners referred the remaining 30% of the patients included in this analysis directly to our centre.

Syncope was defined as a transient loss of consciousness with loss of postural muscle tone, and presyncope as the sensation of near fainting, sometimes accompanied by dizziness, blurred vision, auricular fullness, sweating, and palpitations.<sup>5</sup>

### Evaluation of the patients

We took a clinical history and carried out a physical examination on each patient. The latter included orthostatic blood pressure measurement, standard ECG,<sup>6</sup> and tilt testing, which was done in the morning under fasting conditions.

Tilt testing consisted of subjecting the patient to a 70° tilt for 40 minutes<sup>7–8</sup> while monitoring the ECG continuously and measuring arterial blood pressure non-invasively beat to beat with a photoplethysmograph (Ohmeda Finapres 2300).<sup>9</sup> Tilt testing was considered positive if symptoms of presyncope or syncope occurred, accompanied by a fall in arterial pressure or heart rate (with or without asystoles). Haemodynamic profiles were obtained.<sup>10–11</sup> The patient's tolerance to orthostasis was based upon blood pressure and heart rate responses to tilt testing. Orthostatic intolerance was defined when orthostatic hypotension,<sup>12</sup> postural tachycardia syndrome (POTS),<sup>13</sup> or cardiovascular instability related to respiratory activity occurred.

Patients with negative tilt testing responses, who were older than 50 years, or who had diabetes or other autonomic nervous system (ANS) diseases underwent carotid sinus massage and assessment cardiovascular reflexes. The latter included deep breathing, the 30:15 manoeuvre,<sup>14</sup> the Valsalva manoeuvre, and the handgrip test.<sup>14</sup>

**Abbreviations:** ANS, autonomic nervous system; POTS, postural tachycardia syndrome

The diagnosis of syncope of uncertain origin was based on the absence of syncope related factors in the clinical history, a negative tilt test response, and a negative dysautonomic response.

### Statistical analysis

One way analysis of variance (ANOVA) analysed age differences among the groups. A two sample follow up *t* test was used when differences were found. We used  $\chi^2$  tests to analyse sex differences between the groups. All reported probability (*p*) values were based on two tailed statistical tests, with a significance level of 0.05. The statistical analyses were done using Stat View for windows, version 5.0.1.

### RESULTS

The mean (SD) age of the patients was 41.1 (19.1) years, range 7 to 86; 231 patients were male and 290 female. The men were older ( $p \leq 0.001$ ) than the women, at 46.6 (19.2) v 37.4 (19.1) years, respectively.

Causes of syncope remained unknown in fewer than one third of the patients (fig 1). No differences in age ( $p = 0.21$ ) or sex ( $p = 0.64$ ) were found between patients with unknown and known causes of syncope.

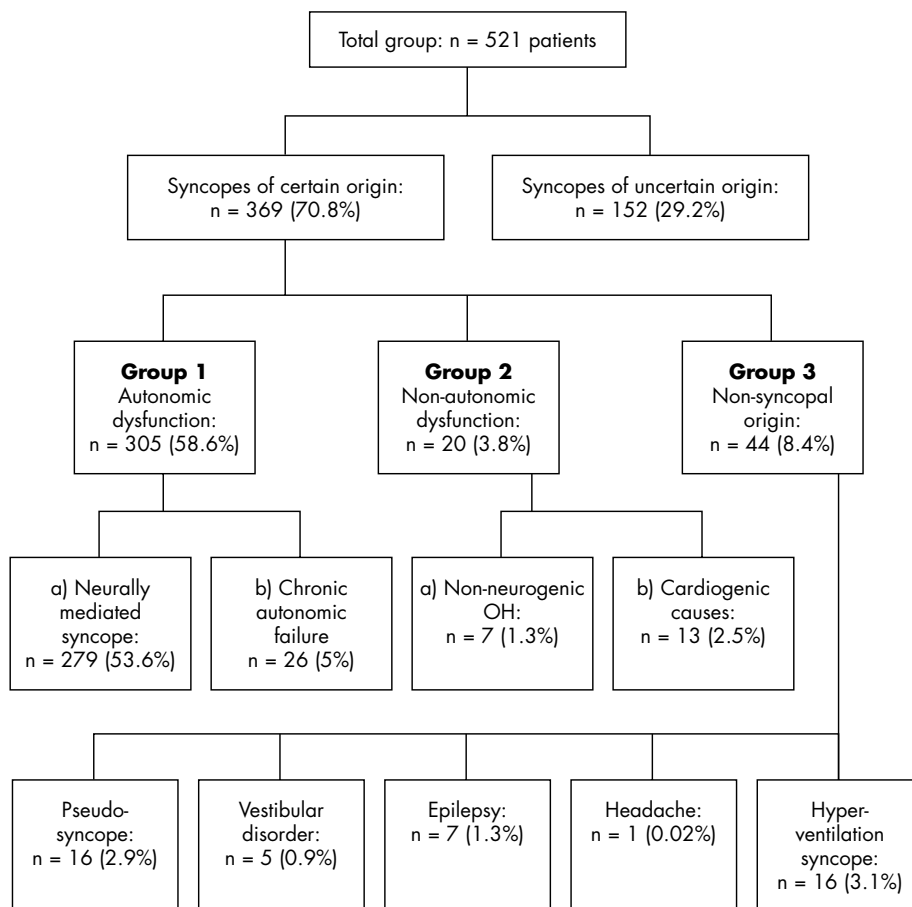
There were three groups of patients with known causes of syncope: those with syncope related to autonomic dysfunction (group 1), those with syncope not related to autonomic dysfunction (group 2), and those with loss of consciousness of non-syncopal origin (group 3). Patients without autonomic dysfunction (age 59.4 (14.6) years; 12 men, 8 women) were older ( $p \leq 0.001$ ) than those who had autonomic dysfunction (age 38.4 (19.0) years; 143 men, 162

women) and those with loss of consciousness of non-syncopal origin (age 38.1 (15.7) years; 11 men, 33 women). A greater proportion of women was found in groups 1 ( $p = 0.006$ ) and 2 ( $p = 0.007$ ) compared with group 3. No differences in sex distribution were observed between groups 1 and 2 ( $p = 0.25$ ).

Table 1 gives the causes of syncope in the three groups of patients. Patients with neurally mediated syncope (group 1a, mean age 36.9 (11.2) years) were younger ( $p \leq 0.001$ ) than patients with chronic autonomic failure (group 1b, mean age 66.8 (17.5) years). No differences were observed in sex distribution between these two groups. Several triggers were identified as causative of neurally mediated syncope in the patients in group 1a. The diagnosis of vasovagal syncope was based on clinical history and positive tilt testing in 83 patients (58.5% with vasodepressor type response, 6.5% with cardioinhibitory type response, and 35% with mixed type response). In the remaining 164 patients, the response to tilt testing was negative and the diagnosis relied exclusively on the clinical history. Tilting disclosed orthostatic intolerance resulting from POTS in 46 subjects (20%), and cardiovascular instability was a frequent finding in the remaining 118 subjects, thus substantiating the diagnosis of neurally mediated syncope. Five patients had both epilepsy and vasovagal syncope. Given the type of seizure and the positive HUT response, these patients were included in group 1a.

### Syncope in patients diagnosed with seizure

Of 521 patients, 18 who were originally diagnosed with epilepsy and were undergoing antiepileptic drug treatment



**Figure 1** Causes of syncope in the patient cohort. The figure summarises the proportion of patients affected by different types of syncope.

**Table 1** Demographic characteristics of patients with different causes of syncope

Cause of syncope	n (%)
<b>Group 1a: Neurally mediated syncope</b>	
Vasovagal syncope	247 (47.4%)
Situational neurally mediated syncope	19 (3.6%)
Carotid sinus hypersensitivity	13 (2.5%)
<b>Group 1b: Chronic autonomic failure</b>	
Definite/severe dysautonomia (orthostatic hypotension)	19 (3.6%)
Initial dysautonomia (parasympathetic)	7 (1.3%)
<b>Group 2a: Non-neurogenic orthostatic hypotension</b>	
Iatrogenic causes	4 (0.8%)
Volume depletion	2 (0.4%)
<b>Group 2b: Cardiogenic syncope</b>	
Paroxysmal atrial fibrillation	4 (0.7%)
Ventricular arrhythmia	5 (0.9%)
Sick sinus syndrome	3 (0.5%)
Aortic valve disease	1 (0.1%)
<b>Group 3: Non-syncopal origin</b>	
Psychogenic conditions	15 (2.9%)
Hyperventilation	16 (3.1%)
Others	14 (2.9%)

were referred to our centre for a second opinion. Epilepsy was confirmed as the cause of loss of consciousness in five of these 18 patients (28%).

Of the remaining 13 patients, one (6%) was diagnosed as having epilepsy associated with vasovagal syncope and was included in group 1a. Given the type of seizure, syncope was considered to be the cause of loss of consciousness in this individual. In the remaining 12 patients (67%) the diagnosis of epilepsy was not confirmed. Ten patients met criteria for a diagnosis of neurally mediated syncope without epilepsy (group 1a). One patient was diagnosed as having neurogenic orthostatic hypotension (group 1b). The cause of the syncope remained unknown in the last patient.

## DISCUSSION

Causes of syncope were found in nearly 70% of patients retrospectively evaluated in our study. Syncope originated from ANS dysfunction in more than 50% of the patients, mostly through a neurally mediated mechanism.<sup>7,15</sup> As expected, patients with ANS dysfunction were predominately female and were younger than those without ANS dysfunction.

A minority of patients with ANS dysfunction had chronic autonomic failure. Seven of these individuals did not have orthostatic hypotension. Thus the diagnosis of chronic autonomic failure was based on impairment of sinoatrial parasympathetic regulation revealed by the Valsalva manoeuvre and deep breathing. Despite the absence of orthostatic hypotension, all these seven patients complained of pre-syncopal and syncopal attacks, presumably because of an impairment of peripheral sympathetic regulation that was not revealed by clinical cardiovascular reflex testing. These findings support the hypothesis that impaired sympathetic regulation may be present from the earliest stages of dysautonomia, preceding impairment of parasympathetic neuroregulation.<sup>16</sup>

Autonomic cardiovascular function tests identified several other causes of abnormal pressure regulation, including non-neurogenic orthostatic hypotension caused by hypotensive drug treatment and volume depletion. For some patients in whom ECG monitoring failed to disclose any structural

abnormalities that might cause syncope and in whom tilt testing did not identify ANS dysfunction, a stress ECG test and electrophysiological studies revealed a cardiac abnormality (for example, an arrhythmia) related to the syncopal event.

Tilt testing helped to identify patients with psychiatric conditions such as panic attacks, depression, hysteria, and cyclothymia mimicking ANS related syncope.<sup>17,18</sup>

The cause of syncope remained uncertain in 29% of the patients. Though this is in keeping with previous studies,<sup>15,19</sup> the proportion was somewhat higher than expected. This may be explained by the fact that patients were seen by physicians at our centre once cardiac abnormalities had been ruled out, so our cohort had a degree of preselection.

With the approach used in the present analysis, we were able to rule out epilepsy as the cause of syncope in a small group of patients who were receiving antiepileptic drugs at the time of their first visit to our centre.<sup>20</sup> Though more data are needed to confirm these findings, our results underline the need for a more accurate clinical approach aimed at differentiating epilepsy from neurally mediated syncope.<sup>21,22</sup> Neurologists should consider syncope caused by ANS failure as a comorbidity factor in most patients with seizures whose clinical characteristics are not straightforward.<sup>2</sup>

A drawback of the present study was the retrospective data collection and the cross sectional design. A prospective controlled study is required to strengthen the validity of our findings. Nevertheless, given the sample size, we believe that our findings provide useful information for neurologists faced with diagnosing a syncope event.

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