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Prevalence and Clinical Factors of Anxiety and Depression in Neurally Mediated and Unexplained Syncope

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Purpose: Several studies have demonstrated that psychiatric disorders such as anxiety, depression and panic attack are associated with syncope, especially vasovagal and unexplained syncope (US). The aim of this study was to compare the prevalence of anxiety and depression between patients with neurally mediated syncope (NMS) and US and to investigate the clinical factors associated with anxiety and depression. **Materials and Methods:** Between January 2009 and March 2010, 383 patients with syncopal episodes completed a Hospital Anxiety and Depression Scale questionnaire to assess symptoms of anxiety and depression. Inclusion criteria were NMS and US. Exclusion criteria were cardiac syncope, orthostatic hypotension and other disorders mimicking syncope. After exclusion, 199 patients were included. **Results:** There were 176 (88.4%) NMS patients and 23 (11.6%) US patients. The prevalence of abnormal anxiety and depression were not significantly different between the NMS and US groups (10.2% vs. 8.7%, *p*=0.99; 8.5% vs. 17.4%, *p*=0.24). Clinical factors associated with anxiety were female gender (*p*=0.01) and six or more recurrent syncopal episodes (*p*=0.01) by univariate analysis. The only factor associated with abnormal anxiety score (OR=20.26, 95% CI: 1.4-291.6, *p*=0.01) was more than six recurrent syncopal episodes, while a positive head-up tilt table testing response was inversely associated with abnormal depression score (OR=0.28, CI: 0.08-0.97, *p*=0.04) in the multiple logistic regression analysis. **Conclusion:** Anxiety was associated with frequent syncopal episodes. Thus, anxiety might be considered in the management of syncope patients.

Key Words: Anxiety, depression, syncope

INTRODUCTION

Syncope is defined as a transient loss of consciousness and postural tone caused by global cerebral hypoperfusion. Recovery is spontaneous, complete, and rapid. The incidence of syncope ranges from 3% to 35% over a person's lifetime.[1,2] However, a substantial number of patients experience recurrent syncopal episodes. Recurrent syncope can cause functional impairment in addition to physical and psychiatric impairment.[3] Recurrent syncope may also increase the incidence of anxiety or mood disorders.[4] Several studies have demonstrated that psychiatric disorders are

especially associated with recurrent vasovagal syncope (VVS) or unexplained syncope (US).[4-8] The prevalence of psychiatric disorders in patients with VVS or US is reported to be higher than average and these psychiatric disorders affect the response to treatment for syncope as well as predicting syncopal recurrence in US[8,9] and VVS.[4,6,10] However, little evidence is available for evaluating the prevalence of anxiety and depression between neurally-mediated syncope (NMS) and US, or pursuing related clinical factors in Korean patients with syncope.

The aim of this study was to compare the prevalence of anxiety and depression between people with NMS and US and to investigate the clinical factors associated with anxiety and depression in affected patients.

MATERIALS AND METHODS

Study population

Three hundred and eighty-three consecutive patients with syncopal episodes who visited the emergency room or outpatient department of Samsung Medical Center, Seoul, Korea were prospectively enrolled between January 2009 and March 2010. Inclusion criteria were NMS syncope (including VVS and situational syncope) and US. Exclusion criteria were cardiac syncope or orthostatic hypotension; another disease causing transient unconsciousness such as cerebrovascular disease including acute cerebral infarction and transient ischemic attacks; seizure; hypoglycemia; drug intoxication; benign paroxysmal positional vertigo; and hyperventilation syndrome. Among the 383 enrolled patients, 86 were excluded because of cardiac syncope (23 patients), orthostatic hypotension (36 patients), lack of a complete evaluation (24 patients), or lack of true syncope (3 patients). In addition, 98 patients declined participation in the questionnaire survey. Therefore, 199 patients were included in this study. Informed consent was obtained from each patient before participation. The study was approved by the regional ethics committee in medical research for the evaluation of syncope.

Evaluation of syncope

All patients underwent detailed medical history documentation and a complete physical examination. An electrocardiogram, echocardiography, head-up tilt table testing (HUT), and 24-hour ambulatory holter monitoring were performed when clinically indicated. According to ESC guidelines,[11] NMS refers to conditions in which an abnormal cardiovas-

cular reflex occurs in response to a trigger, resulting in syncope. NMS is classified into VVS, situational syncope, carotid sinus syncope, and atypical forms of syncope, based on the trigger. VVS is the most common cause of NMS. Clinical features indicating NMS for this study were absence of heart disease, long history of recurrent syncope, occurrence of syncope after sudden unexpected unpleasant sight, sound, smell or pain, prolonged standing or crowding, hot places, or presence of prodromal symptoms such as nausea or vomiting associated with syncope. After cardiac syncope and orthostatic hypotension were excluded by a complete work up, NMS was diagnosed based these clinical features. Situational syncope was diagnosed if syncope occurred during or immediately after specific triggers such as coughing, sneezing, gastrointestinal stimulation, micturition. Clinical features indicating US for this study were syncope without apparent trigger and/or lack of prodromal symptoms, irrespective of HUT results. When a thorough medical history did not suggest NMS, US was diagnosed if the exact mechanism of syncope was still unknown or uncertain at the end of a complete work-up. Syncope-related injury was defined as any physical trauma secondary to syncope that was sufficiently clinically relevant to be mentioned in the patient's medical records. Syncope related to minor injury was defined as swelling, ecchymosis or bruising, abrasion or laceration, and hematoma or minor bleeding. Syncope-related major injury was defined as a major bone segment fracture such as of the skull, causing intracranial hemorrhage and tooth subluxation. Prodromal symptoms were defined as symptoms of autonomic activation that occurred before unconsciousness such as sweating and pallor; cardiopulmonary symptoms such as dyspnea, palpitation or chest discomfort; gastrointestinal symptoms such as indigestion, nausea, vomiting, sensation of defecation, and abdominal pain or discomfort; and cerebral hypoperfusion symptoms such as dizziness, weakness, extreme fatigue and vertigo.

Head-up tilt test protocol

HUT was performed in patients who fasted for 4 hours in a quiet room. After 10 min of supine rest, the patient was tilted upright to 70 degrees for 30 minutes with a footboard used for weight bearing. Blood pressure and electrocardiographic rhythm were monitored at baseline and during HUT. If syncope or presyncope were not induced, an isoproterenol infusion was started at a rate of 1 μg/min without returning the patient to the supine position; infusion rate was

increased every 3 minutes to achieve an increase of 20% above the baseline heart rate for 15 minutes. A positive HUT was defined as induction of presyncope or syncope associated with a systemic hypotension (decrease in systolic blood pressure ≤80 mm Hg or a fall in systolic blood pressure from a baseline value ≥20 mm Hg) and/or bradycardia (heart rate <45/min or heart rate <60/min during isopoterenol infusion).[12]

Evaluation of anxiety and depression

All patients completed the self-administered Hospital Anxiety and Depression Scale (HADS) questionnaire[13] of 14 items measuring the severity of current anxiety and depression, which is used extensively in medical settings. The HADS questionnaire consists of two subscales, one that measures anxiety (HADS-A) and another that measures depression (HADS-D). Each subscale is composed of seven items that are individually scored on a four-point scale from 0 to 3. Scores for each scale range from 0 to 21; higher scores indicate greater anxiety and depression. Total scores were divided into three categories: normal (0-7), borderline (8-10) and abnormal (11-21).

Statistical analysis

Data are expressed as the median with an interquartile range or mean with standard deviation. Comparisons between groups were performed with a Student's t-test for continuous variables and a chi-square test for categorical data. To determine the independent predictors for abnormal anxiety and depression according to the HADS, multivariate logistic regression analysis was performed. Clinical variables associated with abnormal anxiety and depression with a $p \leq 0.2$ in the univariate analysis and could be related with psychiatric disorders such as syncope related injury, age, family history of syncope, and HUT response were introduced into the multivariate model. Bonferroni correction was used to adjust for multiple comparisons. Values of $p < 0.05$ were considered significant. Statistical analyses were performed with SPSS 18.0 (SPSS Interactive Graphics, Version 18.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of study subjects

The clinical baseline characteristics of the study population are in Table 1. The study population was 199 patients (118

female, 59.3%) with a mean age of 40±15 years (range 16-77). The median number of syncopal episodes was two (1-3). One hundred and twenty-one patients (60.8%) had at least one recurrent syncopal episode. In addition, 121 patients (60.8%) visited the emergency room as the initial presenting site, and the other patients visited the outpatient department. Prodromal symptoms were frequently observed in 164 patients (82.4%). Specifically, 94 patients (47.2%) had no injury, 96 (48.2%) had a minor injury, and nine patients (4.5%) had a major injury. A family history of syncope was noted for 22 patients (11.1%). HUT was performed for 133 (66.8%) patients-of whom 96 (72.1%) showed a positive HUT reponse. Underlying diseases were hypertension (12.6%), hyperlipidemia (4.5%), diabetes mellitus (3.5%), hypothyroidism (2.0%), benign prostate hypertrophy (0.5%) and previous history of stroke (1.5%).

Table 1. Baseline Clinical Characteristics of the Study Population

	Values
Age (yrs)	40.09±15.58
Sex, n (%)	
Female	118 (59.3)
Male	81 (40.7)
Presenting site, n (%)	
OPD	77 (39.2)
ER	121 (60.8)
Number of syncope episodes (median)	2 (1-3)
1	78 (39.2)
2-5	99 (49.7)
≥6	22 (11.1)
Prodromal symptom, n (%)	164 (82.4)
Injury, n (%)	
No injury	94 (47.2)
Minor injury*	96 (48.2)
Major injury†	9 (4.5)
Family history of syncope, n (%)	22 (11.1)
Underlying disease, n (%)	
Hypertension	25 (12.6)
Hyperlipidemia	9 (4.5)
Diabetes mellitus	7 (3.5)
Hypothyroidism	4 (2.0)
Previous stroke	3 (1.5)
BPH	1 (0.5)
HUT performed, n (%)	133 (66.8)
Positive response	96 (72.1)

OPD, outpatient department; ER, emergency room; BPH, benign prostatic hypertrophy; HUT, head up tilt table test.
*Contusion, laceration, bruise.
†Bone fracture, tooth subluxation, brain hemorrhage.

Comparison of anxiety and depression between NMS and US

Of the 199 patients in the study population, 176 (88%) were diagnosed with NMS and 23 (12%) were diagnosed with US. Clinical variables and HADS scores in the NMS and US groups are shown in Table 2. Patients with US tended to be older (54±15 vs. 38±14; $p<0.01$) and male (65% vs. 37.5%; $p=0.01$). In addition, patients with US had fewer prodromal symptoms (65.2% vs. 84.7%; $p=0.03$) and a higher prevalence of hypertension (39.1% vs. 9.1%; $p<0.01$) compared to the NMS group.

The median HADS scores for anxiety and depression were five (3-8) and five (3-7) in the NMS group and five (2.5-7.5) and five (2-8.5) in the US group, respectively. The median HADS scores were not significantly different for anxiety ($p=0.83$) or depression ($p=0.70$) between the NMS and US groups. In the NMS group, 18 patients (10.2%) had an abnormal anxiety score, 29 (15.9%) had borderline anxiety, 15 (8.5%) had an abnormal depression score, and 28 (24.4%) had borderline depression. In the US group, two patients (8.7%) had an abnormal anxiety score, three (13.0%) had borderline anxiety, four (17.4%) had an abnormal depression score, and seven (30.4%) had borderline depression. The prevalence of abnormal anxiety and depression were not significantly different between the two groups (10.2% vs. 8.7%; $p=0.99$, 8.5% vs. 17.4%; $p=0.24$). Compared to the general Korean population, in previous studies,[14] the prevalence of anxiety (8.9% vs. 10.2% vs. 8.7%; $p=0.70$) was not significantly different in patients with NMS and US. However the prevalence of depression was lower in the NMS group than in the general Korean population (8.5% vs. 16.1%; $p=0.02$).

Clinical factors associated with anxiety

The clinical factors of age, sex, family history of syncope, number of syncope episodes, HUT response, syncope-related injury, and underlying disease were analyzed between abnormal and normal-to-borderline anxiety groups. Compared to the normal-to-borderline group, patients with abnormal anxiety scores were generally younger, female, more likely to have a family history of syncope, more prodromal symptoms, and had more recurrent episodes of syncope.

Table 2. Comparison of Clinical Variables in Neurally Mediated and Unexplained Syncope

	Neurally mediated syncope (n=176)	Unexplained syncope (n=23)	p value
Age (yrs)	38.21±14.56	54.43±15.96	<0.01
Male, n (%)	66 (37.5)	15 (65.2)	0.01
Family history of syncope, n (%)	18 (10.2)	4 (17.4)	0.29
Number of syncope episodes (median)	2 (1-3)	2 (1-4)	
More than six syncope episodes, n (%)	19 (10.8)	3 (13.0)	0.72
Prodromal symptom, n (%)	149 (84.7)	15 (65.2)	0.03
Injury, n (%)			0.12
No injury	85 (48.3)	9 (39.1)	
Minor injury	85 (48.3)	11 (47.8)	
Major injury	6 (3.4)	3 (13.0)	
Underlying disease, n (%)			
Hypertension	16 (9.1)	9 (39.1)	<0.01
Diabetes mellitus	4 (2.3)	3 (13.0)	0.18
Hyperlipidemia	7 (4.0)	2 (8.7)	0.99
Previous stroke	1 (0.6)	2 (8.7)	0.18
Hypothyroidism	4 (2.3)	0	0.99
BPH	1 (0.6)	0	0.99
HADS scale			
HADS-A (median)	5 (3-8)	5 (2.5-7.5)	0.83
HADS-D (median)	5 (3-7)	5 (2-8.5)	0.70
Borderline anxiety, n (%)	29 (15.9)	3 (13.0)	0.99
Abnormal anxiety, n (%)	18 (10.2)	2 (8.7)	0.99
Borderline depression, n (%)	28 (24.4)	7 (30.4)	0.40
Abnormal depression, n (%)	15 (8.5)	4 (17.4)	0.24

BPH, benign prostatic hypertrophy; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

Significant clinical factors associated with abnormal anxiety were being female (85% vs. 56.4%; p=0.01) and more than six recurrent syncopal episodes (30% vs. 8.9%; p=0.01) in univariate analysis (Table 3). Furthermore, a history of more than six recurrent syncopal episodes (OR=20.26, CI: 1.4-291.6, p=0.01) was a clinical factor associated with abnormal anxiety by multiple logistic regression analysis (Table 4).

Clinical factors associated with depression
Patients with abnormal depression scores were typically women with a greater family history of syncope, more prodromal symptoms, and decreased positive HUT response compared with the normal-to-borderline group. However, these clinical factors were not significant (Table 5). In the multivariate analysis, positive HUT response (OR=0.25, CI: 0.07-0.89, p=0.03) was inversely associated with the abnormal depression score (Table 6).

DISCUSSION

This study revealed that the prevalence of abnormal anxiety and depression measured using HADS were 10.2% and 8.5% for NMS and 8.7% and 17.4% for US, respectively. The prevalence of abnormal anxiety and depression were not significantly different between these groups. Only a history of more than six recurrent syncopal episodes was significantly associated with an abnormal anxiety score. A positive HUT response was inversely associated with an abnormal depression score.

When we compared the patients' HADS scores to the general Korean population of 500 men and 500 women ≥20 years of age from a previous study,[14] we found that syncopal patients had a similar prevalence of anxiety to the general Korean population. Additionally, we found a lower

Table 3. Comparison of Clinical Factors between Normal-to-Borderline and Abnormal-Anxiety Groups (HADS-A)

	Normal to borderline anxiety score group (0-10) (n=179)	Abnormal anxiety score group (11-21) (n=20)	p value
Age (yrs)	40.37±15.70	37.50±14.55	0.43
Female, n (%)	101 (56.4)	17 (85.0)	0.01
Family history of syncope, n (%)	18 (10.1)	4 (20.0)	0.24
More than six syncope episodes, n (%)	16 (8.9)	6 (30.0)	0.01
HUT positive, n (%)	87 (73.1)	9 (69.2)	0.75
Prodromal symptom, n (%)	145 (81.0)	19 (95.0)	0.09
Injury, n (%)			0.53
No injury	86 (48.0)	8 (40.0)	
Minor injury	854 (46.9)	12 (60.0)	
Major injury	9 (5.0)	0	
Underlying disease, n (%)			
Hypertension	23 (12.8)	2 (10.0)	0.99
Diabetes mellitus	5 (2.8)	2 (10.0)	0.84
Hyperlipidemia	8 (4.5)	1 (5.0)	0.99
Previous stroke	3 (1.7)	0	0.99
Hypothyroidism	4 (2.2)	0	0.99
BPH	1 (0.6)	0	0.99

HUT, head up tilt table test; BPH, benign prostatic hypertrophy.

Table 4. Multiple Logistic Regression Analysis for Predicting Abnormal Anxiety

	Odds ratio	95% confidence interval	p value
Age	0.98	0.93-1.03	0.54
Female	3.94	0.66-23.37	0.13
Prodromal symptoms	1.48	0.10-21.53	0.77
More than six syncope episodes	20.26	1.40-291.64	0.01
HUT positive	0.74	0.16-3.36	0.70
Family history of syncope	2.90	0.61-13.64	0.17
Injury	1.28	0.34-4.85	0.70

HUT, head up tilt table test.

Table 5. Comparison of Clinical Factors between Normal-to-Borderline and Abnormal Depression Score Groups (HADS-D)

	Normal to borderline depression score group (0-10) (n=180)	Abnormal depression score group (11-21) (n=19)	p value
Age (yrs)	40.17±15.54	39.26±16.36	0.81
Female, n (%)	104 (57.8)	14 (73.7)	0.18
Family history of syncope, n (%)	19 (10.6)	3 (15.8)	0.44
More than six episodes of syncope, n (%)	20 (11.1)	2 (10.5)	0.99
HUT positive, n (%)	89 (75.40)	7 (50.0)	0.05
Prodromal symptom, n (%)	146 (81.1)	18 (94.7)	0.20
Injury, n (%)			0.63
No injury	86 (47.8)	8 (42.1)	
Minor injury	85 (47.2)	11 (57.9)	
Major injury	9 (5.0)	0	
Underlying disease, n (%)			
Hypertension	23 (12.8)	2 (10.5)	0.99
Diabetes mellitus	6 (3.3)	1 (5.3)	0.99
Hyperlipidemia	9 (5.0)	0	0.99
Previous stroke	3 (1.7)	0	0.99
Hypothyroidism	4 (2.2)	0	0.99
BPH	1 (0.6)	0	0.99

HUT, head up tilt table test; BPH, benign prostatic hypertrophy.

Table 6. Multiple Logistic Regression Analysis for Predicting Abnormal Depression

	Odds ratio	95% confidence interval	p value
Age	0.98	0.94-1.03	0.59
Female	1.47	0.40-5.41	0.55
Prodromal symptom	4.40	0.44-43.17	0.20
More than six syncope episodes	0.88	0.12-6.12	0.90
HUT positive	0.25	0.07-0.89	0.03
Family history of syncope	1.53	0.33-7.09	0.58
Injury	2.06	0.59-7.21	0.25

HUT, head up tilt table test.

prevalence of depression in the NMS group compared with the general population, for whom abnormal anxiety occurred in 8.9% and depression was seen in 16.1%. These findings are contrary to the results of previous studies that found that the prevalence of psychiatric disease is higher than average in patients with either recurrent US[8,9,15] or VVS.[7] This difference might be due to the fact that the median number of syncopal episodes in our study was only two, syncope-related major injury was not frequently observed, patients acknowledged their episodes of syncope as benign. This could be because education regarding awareness and possible avoidance of trigger and knowledge of maneuvers such as supine positioning at early recognition of prodromal symptoms were often successful.

Our results showed that female gender and a history of more than six syncopal episodes might be closely related to greater anxiety, by subgroup analysis. These results corre-

spond to previous studies reporting that anxiety might be associated with recurrent VVS and US,[5,6,8,16,17] a psychiatric factor frequently reported in females[6,15,18] and a risk factor for syncopal recurrence in US[8] and VVS.[7] Nevertheless, whether anxiety was a cause or consequence of recurrent syncope is unclear. We noted that anxiety of episode anticipation was increased in patients with recurrent syncope, and hypothesized that this anxiety might be the cause of increased sympathetic tone through enhancement of catecholamine release and direct central nervous system modulation,[5] thereby triggering an excessive parasympathetic response associated with bradycardia and inappropriate reflex vasodilation. This mechanism could explain how anxiety causes recurrent syncope, and vice versa. Thus, relief of anxiety might be a supportive treatment modality for this cycle.[18]

This study has several limitations. First, the degree of anxiety and depression measured by HADS might not reflect

the incidence of clinical anxiety and depression. Although numerous studies have used HADS questionnaires to determine the prevalence of anxiety and depression,[10,14,16,19] whether this diagnostic tool is reliable and accurate for measuring actual anxiety and depression remains uncertain. Second, the control group was not extracted from our study population. The control group was adapted from cases published in previous studies, and was used to compare reference data in general and cancerous populations.[14] Finally, we focused on the influence of anxiety and depression in our study, however other psychiatric disorders related to syncope including panic disorder, mood disorder, and somatization were not considered.

In conclusion, the prevalence of anxiety and depression were not different for NMS and for US. However, anxiety was associated with frequent syncopal episodes. Thus, the addition of anxiety management in syncope patients could be beneficial in preventing future syncope episodes.

ACKNOWLEDGEMENTS

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