Medically Unexplained Syncope and its Relationship to Psychiatric Disorders

André Gomes Andrighetto, Ângela Beatriz John, Juarez Neuhaus Barbisan, José Geraldo Vernet Taborda

Porto Alegre, RS - Brazil

Currently, a series of diagnostic tests are available for investigating syncopal episodes. However, in approximately 30% of patients with syncope, the extensive investigations fail to reveal a definite etiology. Recent evidence suggests that a significant portion of these patients may suffer from psychiatric illnesses that lead to recurrent syncope. In the present review, the authors discuss the relationship between medically undetermined syncope and psychiatric illnesses, such as major depression, panic, anxiety and somatization disorders. The patients most likely to develop syncope as a result of psychiatric illnesses are primarily women under the age of 40 years, with multiple previous syncopal episodes and marked presyncopal symptomatology. Although psychiatric syncope should be considered an exclusion diagnosis, it should be remembered, as the referral to a specialist for the institution of a therapy targeting the baseline disease leads to a better prognosis and decreases the occurrence of syncopal episodes.

Syncope is defined as a sudden and transient loss of both consciousness and postural tone, with subsequent complete and spontaneous recovery, which does not require cardiopulmonary resuscitation [1]. It is the clinical result of the critical and transient decrease of blood flow to the neurons responsible for maintaining consciousness [2].

Syncope is a frequent condition, accounting for 1% to 6% of all hospital admissions and for 3% of the visits to the emergency department in the United States [3]. In the Framingham Study [4], which evaluated a cohort study of more than 5,000 patients during 26 years of follow-up, Savage et al suggest that approximately 3% of the population will experience a syncopal episode during their lives. The incidence of this condition can be even higher, approaching 37%, if young patients are evaluated. The prevalence of syncope increases with age, ranging from 0.7% in individuals between 35 and 44 years of age to 5.6% in individuals ≥ 5 years of age. In this same age group, the annual incidence is 6%, with a recurrence rate of 30% [5].

Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia – Porto Alegre
Mailing address: Juarez Neuhaus Barbisan – Av. Princesa Isabel 395 – 90620-001 – Porto Alegre, RS - Brazil

Neurocardiogenic syncope, triggered by the stimulation of intramyocardial receptors, has been recognized as the most frequent, accounting for 50% of the diagnoses [2,6]. The situational syncopes (postmicturition, cough, swallowing or defecation), as well as the carotid sinus syncope, are also neurally mediated. Other possible causes include heart diseases (obstruction and arrhythmias), neurologic diseases (stroke, seizures) and those related to drug use or metabolic disorders (use of vasodilators and hypoglycemia). Thus, the causes of syncope range from benign conditions to potentially fatal diseases. However, in spite of the use of multiple diagnostic tests, in approximately 30% of the patients, a defined etiology for the syncopal episodes is still lacking [7].

Psychiatric illnesses have been underestimated as possible causes of syncope. Actually, results of 3 cohort studies published in the early 80s (fig. 1) show psychiatric diseases accounting for 1% to 7% of all causes of syncope [3,8,9]. However, recent evidence suggests that the prevalence of psychiatric disorders in patients with medically undetermined syncope (MUS) can be as high as 26% [10,11]. In addition, recurrent syncopes resulted in a psychosocial impact similar to that observed in other chronic debilitating diseases [12].

Thus, this review aims to underscore the relationship between syncope and psychiatric illnesses, to describe the patients most likely to develop syncope and to establish the psychosocial and prognostic impact and the specific management of this disease.

Syncope and psychiatric illnesses

Only recently has the relationship between syncope and psychiatric illnesses been studied. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [13] and the Classification of Mental and Behavioral Disorders of the ICD-10 [14] include dizziness or syncope as clinical findings of somatization, anxiety and panic disorders, as well as of psychoactive substance abuse. The ICD-10 includes dizziness as one of the symptoms found in somatoform dysfunction (F45.3) and in generalized anxiety disorder (F41.1) and categorizes psychogenic syncope with other specified neurotic disorders (F48.8). Both the DSM-IV and the ICD-10 include dizziness, vertigo or fainting in the

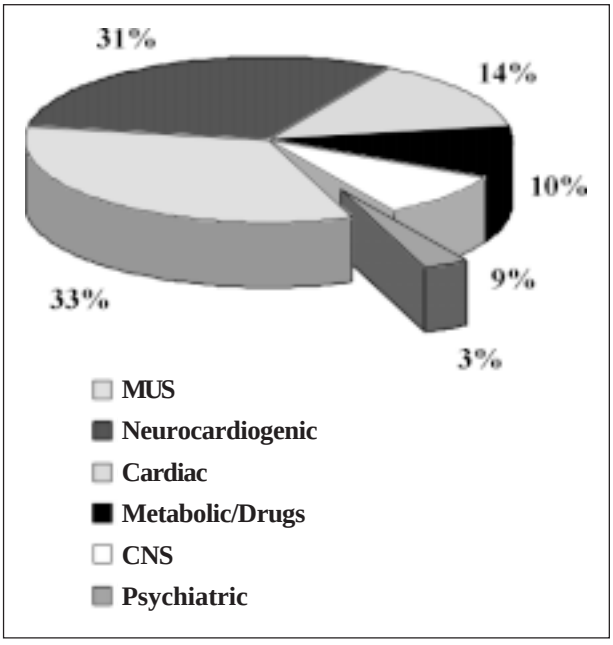

Fig. 1 – Distribution of the different causes of syncope according to 3 cohort studies conducted in the early 80's [3,8,9].

diagnostic criteria for panic disorder (F41.0). Furthermore, patients with major depression usually report some kind of cardiopulmonary complaint or some other physical symptoms, including syncope. Finally, the chronic and excessive abuse of alcohol or other psychoactive substances can also lead to the development of syncope or seizures that are hard to distinguish from syncopal episodes [15]. Orthostatic hypotension (combined or not with the Wernicke encephalopathy) and gastrointestinal bleeding are some of the complications of alcoholism that can lead to the development of syncope. The use of cocaine, sedatives and opiates can also lead to syncope as a result of toxicity, of interaction with alcohol or other medications, and of withdrawal reactions [16].

Kapoor et al [17], examining a cohort of 414 patients with syncope, found that 20% met the criteria for at least one psychiatric disease, such as somatization, generalized anxiety and panic disorder, major depression, and alcohol and drug abuse. Of special interest was the fact that somatization, anxiety and panic disorders were more frequent in patients with MUS than in all the remaining patients with syncope (12% vs 1%, p = 0.01).

In this same study [17], the patients with psychiatric disorders were predominantly females, whereas those suffering from alcohol/drug abuse were predominantly males. When compared with patients with syncope who did not have any psychiatric disorder, those patients with psychiatric disorders were younger, had experienced an increased number of syncopal episodes in the previous year, had suffered from more prodromal symptoms, had reported more complaints and had been less likely to suffer from heart diseases, arrhythmias and cerebrovascular diseases. No difference in the physical trauma resulting from the syncopal episode existed between the 2 groups. The predisposing factors to psychiatric disorders in the patients with syncope were the occurrence of 4 or more episodes of syncope in the previous year (RR, 2.5 and confidence interval [CI], 1.2-5.1) and the presence of presyncopal symptoms (RR, 2.4 and CI, 1.1-5.2), such as migraine, palpitations, abdominal pain, weakness, scotomata, and nausea or vomiting. In addition, being male (RR 7.7 e I.C 2.4-23.8) and under 65 years of age (RR, 4.5 and CI, 2.2-16.1) were strong predictors of alcohol or psychoactive substance abuse.

Linzer et al [10] found similar results. A psychiatric disorder was diagnosed in 24% of the 72 patients seen at the Syncope Clinic of the Duke University, and the most common was the panic disorder followed by major depression. Similarly, the patients with psychiatric symptoms were younger, had suffered from more presyncopal symptoms, had experienced an increased number of syncopal and presyncopal events within the 6 months prior to the evaluation and had suffered from increased dysfunction due to recurrent syncope.

On the other hand, Koenig et al [18] found that psychiatric diseases were the most common cause of syncope in young patients, exceeding even the syncopes of vasovagal origin. Psychiatric diagnoses were established in 39% of the patients studied and included depression, panic and conversion disorder.

It is important to emphasize that many of the presyncopal symptoms reported in the studies just mentioned (table I) are part of the diagnostic criteria for panic disorder [13,14]. Evidence shows that, in 9% of the patients with panic disorder, syncope is the initial presentation of their psychiatric disease [19]. The major findings of the studies mentioned above are summarized in table II.

Diagnosing psychiatric syncope

The importance of MUS resides not only in the fact that it is a frequent condition, but also in view of its morbidity. This corroborates the importance of establishing an etiologic diagnosis whenever possible.

Clinical investigation begins with a thorough medical history and physical examination and an electrocardiogram at rest. Using only these semiotic tools, about 50% of the

Table I – Most frequently reported presyncopal symptoms in patients with syncope caused by psychiatric disorders

Migraine	Palpitations
Abdominal pain	Weakness
Scotomata	Dizziness
Nausea	Vomiting
Chest pain	Tremor
Pallor	Dyspnea

Extracted from [11,17,18]

Table II – Studies linking medically undetermined syncope to psychiatric disorders

Studies	N	Psychiatric syncope as the etiology of the syncope (%)	Most frequent psychiatric disorders	Diagnostic tool
Linzer [10]	72	24	Panic and major depression	Referral to the expert using the DSM-III criteria
Linzer [11]	98	24-31	Panic with or without agoraphobia, Major depression and conversion disorder	SIP SCL – 90 DSM-III-R
Linzer [12]	62	16	Somatization disorders, anxiety and depression	SIP SCL – 90
Kapoor [17]	414	20	Somatization disorders, panic disorder, anxiety and mjor depression	DIS
Koenig [18]	197	39 (16-39 anos) 20 (40-65 anos) 3.6 (>65 anos)	Depression, panic disorder conversion disorder	Referral to expert and hyperventilation maneuver

DSM-III- Diagnostic and Statistical Manual of Mental Disorders, 3rd ed.; SIP- Sickness Impact Profile; SCL- 90- Symptom Checklist 90; DSM-III-R- Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, revised; DIS- Diagnostic Interview Schedule.

patients can have their diagnosis established [3,6,8,20]. If this initial approach fails to reveal a specific etiology, one must proceed with the investigation and evaluate the patients according to the presence or absence of structural heart disease. Such dichotomic approach is valuable, not only to guide the diagnosis, but also to assess the prognosis, as patients with structural heart diseases, when compared with patients with noncardiological causes of syncope or with MUS, have a poorer prognosis due to the increased incidence of sudden death. Actually, the mortality rate in one year of patients with syncope and previous structural heart disease ranged from 18 to 33%, whereas these figures reached 12% in patients with noncardiological causes of syncope and 6% in patients with MUS [8,9,21].

During the investigation of patients with heart diseases, methods such as 24-hour electrocardiographic monitoring (Holter), prolonged monitoring of events, treadmill testing, electrophysiological study, echocardiogram and coronary angiography may be employed. In the absence of structural heart disease or if the previous evaluation fails to reveal any abnormal finding, the tilt-table test is the preferred procedure [2,5]. If a definite diagnosis still cannot be established, the possibility of syncope due to psychiatric disorders must be considered, as, according to Busnello et al [22], the estimated prevalence of psychiatric morbidity in our area is high, reaching up to 49% in the urban area of Porto Alegre (RS). When equivocal and unexplained somatic complaints are present, mainly those related to the cardiopulmonary, gastrointestinal and neurologic systems, the possibility of psychiatric comorbidity should not be forgotten.

Thus, when assessing a patient with a history of recurrent syncope in the long term that lacks a definite etiology in spite of an extensive investigation, female sex, age <40 years, the presence of 4 or more episodes of syncope or presyncope in the previous year and the presence of presyncopal symptoms (table I) are evidence that strongly suggest some kind of psychiatric disorder, mainly panic disorder, as the cause of syncope. Male sex and age <65 years are frequently related to alcohol and other psychoactive drug abuse and to chemical addiction.

The addition of some provocative tests to the clinical features of certain patients may confirm the diagnosis of a suspected psychiatric disorder as the cause of recurrent syncope. In the study of Koenig et al [18], the hyperventilation maneuver, which reproduces the presyncopal symptoms [23], had a positive predictive value of 59% for psychiatric causes of syncope. Also, the tilt-table test [24-26], used to clarify the diagnosis of patients with MUS, specifically for the diagnosis of the neurocardiogenic form, can be useful in the identification of patients with underlying psychiatric disorders. After trying to standardize the methodology to perform the test and to interpret the responses to it [27,28], Hackel et al [29] suggest a new kind of response to the tilt-table test. According to this author, a psychosomatic response would be demonstrated when the patient shows orthostatic intolerance during the test, without significant concomitant hemodynamic abnormalities. These patients would be likely to suffer from underlying psychiatric disorders, usually major depression or anxiety disorder. In these patients, the level of serum catecholamines would show a significant increase seconds before the syncopal episode. During the psychosomatic response, the levels of catecholamines would remain high during the whole test, in contrast to the neurocardiogenic form, where a sudden decrease in the levels of norepinephrine is observed as a result of the sudden decline in the sympathetic nervous system activity and the increase in vagal activity [30]. It should be noted that this finding is not restricted to the psychosomatic response to the tilt-table test, as the postural tachycardia syndrome also shows symptoms of orthostatic intolerance and an increase in heart rate of more than 30 bpm compared with the resting period. This hampers the differential diagnosis between both conditions [31].

However, although the provocative tests might support the suspicion that the syncopal episodes may be due to psychiatric disorders, the diagnosis is established only by a psychiatric interview.

Psychosocial impact and prognosis

In the cohort study by Kapoor [17], patients with at least one psychiatric diagnosis had higher recurrence rates (26.3%) than those without any of these disorders. In fact, the high recurrence rate of syncope during follow-up is consistent with a causal role of psychiatric disorders, as these conditions are not routinely searched for, are usually missed and end up not being treated. In this same study, 52% of the physicians who provided the initial care to the patients missed the diagnosis of psychiatric disorders as a cause of the syncopal episodes.

Taborda [32] studied patients with chronic complaints and reported that approximately 20% to 30% of the costs incurred in basic health care result from patients with multiple or repeated somatic complaints, including patients with recurrent syncope. The extensive diagnostic evaluation provided to these patients represents a major source of expense within the Health Care System and exposes these patients to potentially iatrogenic interventions. As the patients do not find a proper solution in the Health Care System, they return chronically to the outpatient clinics and hospitals due to their unresolved somatic complaints [32].

Although some studies have shown that patients with MUS have a good prognosis in terms of mortality [20] or sudden death [8,9,21], the anxiety generated by the extensive unsuccessful investigation has a marked impact on the prognosis of these patients.

To assess this, a study [12] that measured the degree of functional and physical impact of general medical conditions using the Sickness Impact Profile and the Symptom Checklist 90, showed that the recurrent nature of the syncopes results in a psychosocial impact similar to that observed in chronic diseases, such as rheumatoid arthritis and chronic back pain. When the patients were talking about their symptoms, they mentioned both the degree of severity and the degree of impairment caused by their disease, and the scores of somatization disorder, anxiety and depression were particularly high. When asked about which aspects of their lives were impaired by the recurrent syncopes, 76% of the patients reported that the syncopes interfered with their daily activities, 64% reported that the syncopes interfered with driving, 39% reported that it was difficult to remain on the job and 26% reported some impairment in familiar relationships, such as with the spouse and friends. It was noteworthy that 73% of the individuals interviewed reported symptoms of anxiety or depression due to the recurrent syncopes themselves.

Thus, it is clear that recurrent syncopes may cause a major psychosocial impact and that they may be not only combined with psychiatric disorders but also keep a causal relationship with these diseases, mainly with anxiety and depression disorders. However, whether psychiatric diseases are the cause of syncope or the result of recurrent syncopes in the long-term leading to anxiety, depression and worsening of the psychological status, is not known [10]. The problem is worse when the patients and the physicians keep searching for an organic diagnosis for the symptoms, neglecting possible psychiatric comorbidities.

Management of patients with psychiatric syncope

Once the diagnosis of syncope due to psychiatric disorders in individuals with MUS is suspected, the approach to these patients should include the following: 1) a psychiatric diagnosis made by an expert and further treatment of the comorbidity with 2) the use of psychiatric medication guided by the psychiatrist; 3) the development of groups for the discussion of the disease and the identification of psychosocial stressors; 4) stimulate a better physician-patient relationship and 5) initial care and continuous follow-up in primary care services. Once this management strategy is followed, the decrease or disappearance of the somatic symptoms, as well as the decrease in costs for the health system and the prevention of possible iatrogenic management strategies can be achieved.

With regard to the specific therapy with psychoactive drugs, Hackel et al [29] state that the therapy with clonazepam or fluoxetine reduces the syncopal symptoms in most patients [11]. Thus, the resolution of the symptoms after the institution of psychiatric therapy supports the idea that psychiatric illnesses would not only be related to, but could also account for, the syncopes.

However, whether the better outcome of these patients would be only due to the direct action of the drugs used for the treatment of the underlying psychiatric diseases or to a possible adverse effect that would inhibit the neural mechanisms that trigger the syncopal reflex, is not known. Although it is stated that the specific therapy with psychoactive drugs could reduce the recurrence of the syncopal episodes, this statement does not mean that the psychiatric disorders are the cause of the syncopes, as the mode of action of these drugs is not fully clarified. Additional studies are required.

Conclusion

Syncope and psychiatric disorders seem to be frequently related. Although initially neglected, syncope caused by psychiatric disorders may account for 26% of all etiologies of syncopal episodes that are caused, most of the time, by major depression, and panic, anxiety and somatization disorders. When the investigation of an organic cause fails to reveal any results, the psychiatric disorders must be considered mainly in patients of the female sex, less than 40 years of age, with 4 or more episodes of syncope or presyncope in the previous year and with a marked presyncopal symptomatology. In men under the age of 65 years, the search for alcohol or psychoactive substance abuse and chemical addiction is recommended. The hyperventilation maneuver and the tilt-table testing may be useful in the identification of these patients. Nevertheless, only the psychiatric interview may establish the definite diagnosis.

Once a psychiatric disorder is suspected as the cause

of syncope, the aim should be the diagnosis and specific treatment of this disorder through referral to an expert, as there are reports of remission of the syncopal episodes after the treatment of the actual cause of this disease.

Acknowledgment

We thank Fabiane N. Backes, a medical student, and the Research Unit of the IC-FUC, for their assistance.

References

1. Kapoor WN. Syncope and hypotension. In: Braunwald E - Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed.. Philadelphia: WB Saunders, 1996; cap. 28: 863-75.
2. Hachul D, Scanavacca M. Síncope. Rev Soc Cardiol Est SP 1998: 8: 27-37.
3. Day SC, Cook EF, Funkenstein H, Goldman L. Evaluation and outcome of emergency room patients with transient loss of consciousness. Am J Med 1982; 73:15-23.
4. Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope: The Framingham Study. Stroke 1985; 16: 626-9.
5. Kapoor WN. Diagnostic evaluation of syncope. Am J Med 1991; 90: 91-106.
6. Eagle KA, Pruitt AA. Síncope. In: Cardiologia - The Medical and Surgical Cardiac Units at the Massachusetts General Hospital. 2nd ed.. Rio de Janeiro: Medsi, 1993: 41-57.
7. Sra JS, Anderson AJ, Sheikh SH, et al. Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. Ann Intern Med 1991; 114: 1013.
8. Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. N Engl J Med 1983; 309: 197-204.
9. Eagle KA, Black HR, Cook EF, Goldman L. Evaluation of prognostic classifications for patientes with syncope. Am J Med 1985; 79: 455-60.
10. Linzer M, Felder A, Hackel A, et al. Psychiatric syncope: a new look at an old disease. Psychosomatics 1990; 31: 181-8.
11. Linzer M, Pontinen M, Divine GW, Estes NAM. Medically unexplained syncope: relationship to psychiatric illness. Am J Med 1992; 92(suppl 1A): 1A–18S.
12. Linzer M, Pontinen M, Gold DT, Divine GW, Felder A, Broooks WB. Impairment of physical and psychosocial function in recurrent syncope. J Clin Epidemiol 1991; 44: 1037-43.
13. American Psychiatric Association. Manual de Diagnóstico e Estatística de Transtornos Mentais. Trad. Dayse Batista, 4ª edição revista, DSM-IV. Porto Alegre: Artes Médicas, 1995.
14. World Health Organization - Classificação dos Transtornos Mentais e de Comportamento da CID-10 (Classificação Internacional de Doenças). Descrições Clínicas e Diretrizes Diagnósticas – Coord. Organização Mundial de Saúde. Tradução Dorgival Caetano. Porto Alegre: Artes Médicas, 1993.
15. Kapoor WN. Workup and management of patients with syncope. Med Clin North Am 1995; 79: 1153-70.
16. Kapoor WN, Schulberg HC. Psychiatric disorders in patients with syncope. In: Grubb BP, Olshansky B - Syncope: Mechanisms and Management. New York: Futura Publishing, 1998: Cap. 9: 253-64.
17. Kapoor WN, Fortunato M, Hanusa BH, Schulberg HC. Psychiatric illnesses in patients with syncope. Am J Med 1995; 99: 505-12.
18. Koenig D, Linzer M, Pontinen M, Divine GW. Syncope in young adults: evidence for a combined medical and psychiatric approach. J Intern Med 1992; 232: 169-76.
19. Katon W. Panic disorder and somatization: review of 55 cases. Am J Med 1984; 77:101-6.
20. Silverstein MD, Singer DE, Mulley AG, Thibault GE, Barnett GO. Patients with syncope admitted to medical intensive care units. JAMA 1982; 248: 1185-9.
21. Akhtar M, Jazayeri M, Sra J. Cardiovascular causes of syncope: identifying and controlling trigger mechanisms. Postgrad Med 1991; 90: 87-94.
22. Busnello ED, Pereira MO, Knapp WP, et al. Morbidade psiquiátrica na população urbana de Porto Alegre. J Bras Psiq 1992; 41: 507-12.
23. Herman SP, Stickler GB, Lucas AR. Hyperventilation syndrome in children and adolescents: long-term follow-up. Pediatrics 1981; 67: 183-7.
24. Kenny RA, Bayliss J, Ingram A, Sutton R. Head up tilt: a useful test for investigating unexplained syncope. Lancet 1986; 1: 1352-4.
25. Abi-Samra F, Maloney JD, Fouad-Tarazi FM, Castle L. The usefulness of head-up tilt testing and hemodynamic investigations in the workup of syncope of unknown origin. PACE 1988; 11: 1202-14.
26. Grubb BP, Temesy-Armos P, Hahn H, Elliot L. Utility of upright til-table testing in the evaluation and management of syncope of unknown origin. Am J Med 1991; 90: 6-10.
27. Benditt DG, Ferguson DW, Grubb BP, et al. Acc Expert Consensus Document. Tilt table testing for assessing syncope. J Am Coll Cardiol 1996; 28: 263-75.
28. Brito Júnior HL, Lanna RP, Baraky S. Síncope vasovagal e teste de inclinação: revisão para padronização. Reblampa 1997; 10: 78-86.
29. Hackel A, Linzer M, Anderson N, Williams R. Cardiovascular and catecholamine responses to head-up tilt in the diagnosis of recurrent unexplained syncope in elderly patients. J Am Geriatr Soc 1991; 39: 663-9.
30. Mark AL. The Bezold-Jarish reflex revisted: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983; 1: 90-102.
31. Low PA, Opfer-Gehrking TL, Textor SC, et al. Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. Journal of the Autonomic Nervous System 1994; 50: 181-8.
32. Taborda JGV. O paciente queixoso crônico: contribuição ao diagnóstico multiaxial (Dissertação de Mestrado). Porto Alegre: Universidade Federal do Rio Grande do Sul, 1996.