Clinical Outcome of Patients with Neurocardiogenic Syncope (NCS) After Therapy Interruption

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Objective

To evaluate the outcome of patients with NCS after interruption of pharmacological therapy and to investigate the possible clinical variables predicting recurrence.

Methods

Thirty-seven patients (age 31±16 years) with refractory recurrent NCS being 19 females where prospectively studied. All patients became asymptomatic and had a negative tilt table test (TT) after pharmacological therapy. The treatment was interrupted and one month later, a new TT with no medication was carried out. The probability free of symptoms recurrence was analyzed according to sex, age, number of syncope episodes previously to the treatment, clinical history time, treatment time, drug free from treatment time and TT result.

Results

Twenty-two patients (59%) presented recurrence during a mean follow-up of 21±19.7 months. The variables related to greater recurrence were number of previous syncope (p=0.0248), positive TT after interruption of the therapy (p=0.0002) and female gender (p= 0.0131).

Conclusions

Most of the very symptomatic patients with NCS present recurrence after the suppression of a specific therapy. A TT carried out after treatment discontinuation can identify patients with higher risk of recurrence, specially in the first year of follow-up.

Key words

Vasovagal syncope, tilt -table test, treatment.

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Syncope is a common clinical issue[1,2] and affects both men and women, with an incidence of 3% and 3.5%, respectively[3]. Data of the Framingham's study[4] showed that the vasovagal or neurally mediated syncope (NMS) corresponds to 21.2% of all cases and is not related to increase in the cardiovascular risk, confirming its benignity.

The vasovagal syncope occurs by the sudden development of hypotension and bradicardia due to a deep failure of the cardiocirculatory mechanisms that maintain blood pressure and cerebral perfusion[5,6].

The tilt-table test (TT) is a good tool to identify those patients susceptible to vasovagal syncope[7-11]. Most of the vasovagal episodes is sporadic and easily recognized by their prodromic symptoms and signs[12,13]. However, some patients present not so typical symptoms, what increases the risk of physical injuries[14,15].

The introduction of pharmacological therapy for NMS must be considered in case the general dietetic and behavioral measures do not prevent recurrences and also to improve quality of life[13-16]. The use of TT for the therapeutic follow-up of the neurocardiogenic syncope is controversial, but there are some data supporting a better clinical outcome when a negative TT is achieved after treatment[17-19]. Once initiated, the treatment suppression is empirically carried out and there are no established criteria to evaluate when to do it and how to evaluate patients after the interruption[13,20,21].

The objectives of this study were to evaluate the clinical outcome of very symptomatic patients with NMS after interruption of the specific pharmacological treatment and the possible clinical variables predicting recurrence during the follow-up.

Methods

Patients from the Syncope Unit of Heart Institute –São Paulo University were prospectively evaluated. The inclusion criteria for the study were: history of recurrent syncope (two or more episodes in the previous 12 months); positive response to the tilt-table test; indication of specific pharmacological therapy (presence of symptoms in spite of the general behavioral and dietetic measures); negative tilt in the course of treatment; asymptomatic after therapy.

The exclusion criteria were: history of physical trauma related to the syncope; short or absent prodrome symptoms and risky professional activity.

Thirty-seven patients with average age of 31 $\pm$ 16 years (from 10 to 80 years - median 18) were selected: 19 females (51.35%) and 18 males (48.64%).

The mean history time of syncope was 52.8$\pm$90.7 months (median=24) and the average number of syncope was 3.5$\pm$1.5/year (median=3). The patients were receiving betablockers; fludrocortisone or association of these two drugs. The treatment average time was 27.1$\pm$16.4 months (median=44).

Study design

The selected patients were oriented to discontinue the pharmacological therapy and were then submitted to a tilt table test, 30 days after the discontinuation. The tilt protocol carried out after therapy suppression was identical to the diagnostic test (prolonged baseline)[13]. Regardless of the test result, the patients were maintained with no specific treatment, but with general recommendations (increase of hydro-saline ingestion, elastic stockings, avoiding onset factors and postural education). They were instructed to return to the Outpatient Syncope Unit for routine consultation every three months or immediately in case of syncope recurrence.

Statistical analysis

The variables were described through averages, standard deviations, minimum, maximum and median values, or through absolute and relative frequencies. The patient groups were compared by Student-t and Person and Fisher's Chi-square tests for categorized variables and Wilcoxon's test for independent samples and continuous variables. The probability free of symptom recurrence was estimated by Kaplan-Meier actuarial analysis and compared between the groups by log rank's test[22-24].

Results

The probability free of recurrence observed after therapy supression is described in figure 1.

Most of the patients presented recurrence along the follow-up. After 6 months with no treatment, the event-free probability was estimated to be 77% and 64% after one year. At the end of follow-up however, the symptom-free probability was estimated to be 24%.

Thirteen (35%) patients showed a positive TT response and 24 (65%) patients remained with a negative response to tilt after therapy discontinuation.

When clinical outcome of the patients with positive and negative TT were separately analyzed, a statistically significant difference was observed between them ($p<0.0102$). Most of the patients (84%) with positive tilt test recurred within the first year (figure 2).

The average time for first recurrence in those patients with positive TT was 7.97$\pm$10.37 months and 24$\pm$13.21 months for those with negative TT. ($p=0.00044$).

Among the clinical variables analyzed, it was observed that patients with recurrence showed a higher frequency of previous syncope spells in relation to the asymptomatic ones ($p= 0.0248$) and females were predominant in relation to males ($p=0.0131$). (Table 1).

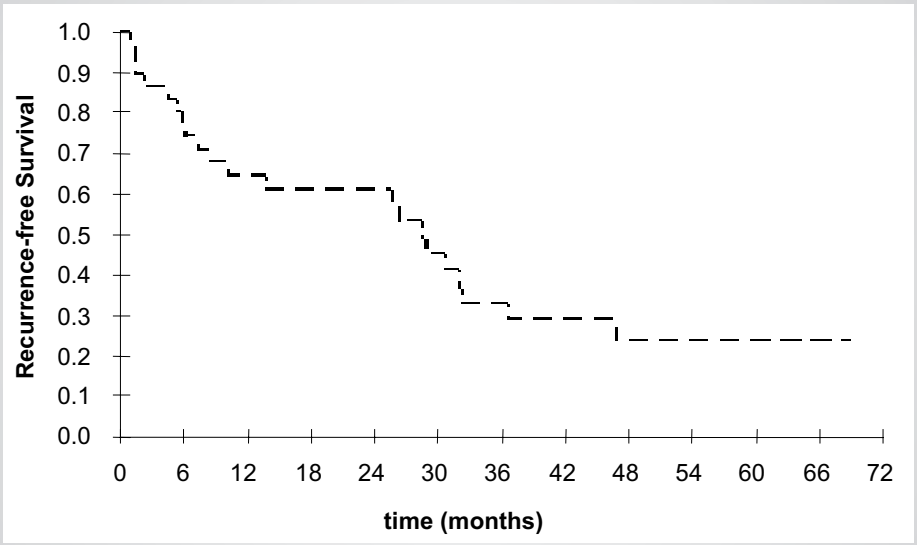

Fig. 1- Recurrence-free probability in the studied population

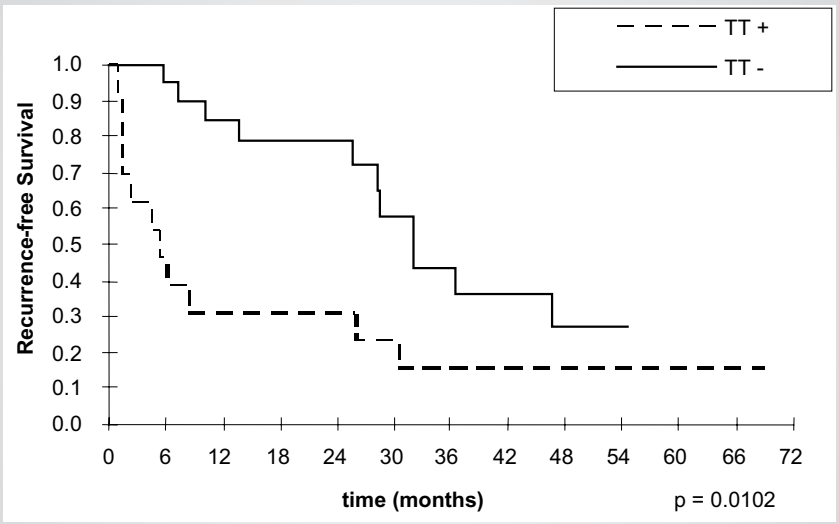

Fig. 2 – Event-free probability curve according to the Tilt Test result after pharmacological therapy suppression

Discussion

The vasovagal syncope is characterized by a functional and intermittent disorder of the autonomic nervous system, which most of the times commits young, cardiologically healthy individuals[1-4]. In general, the majority of patients benefit from general dietetic and behavioral measures, however, pharmacological intervention is required in a specific subgroup in whom symptoms are not adequately controlled[25,26]. Kapoor et al[25-27], observed that accidents were reported in 6% of the patients with NMS, with the smaller injury being laceration. Contusions occurred in 29% of the cases. Another study showed that the recurrent syncope is associated to fractures and soft tissue injuries in 12% of the cases[28].

The positive tilt test identifies individuals susceptible to the vasovagal syncope with a positivity rate between 40 and 60% and with a good diagnostic specificity[9,10,11,13]. The difficulty to predict recurrences has been the ground for several studies in the last few years[29-33], aiming to identifying high- and low-risk patients.

In our study it was observed that 32% of the patients who discontinued therapy recurred within the first follow-up year, increasing to 59% when the average follow-up of 21+19.7 month was considered.

When evaluating patients diagnosed with neurocar-

Table 1 - Clinical characteristics of neurocardiogenic syncope patients with recurrence and asymptomatic ones

Characteristics	Recurrence (22/37)	Asymptomatic (15/37)	p
Gender female	15(68.1%)	4 (26.6%)	0.0131
Age (average in years)	33.09+20.35	29.93+16.58	0.7923
Previous history time (months)	36.91+37.86	31.53+38.02	0.4635
Number of previous syncope episodes	4.5+1.34	3.53+1.36	0.0248
Treatment period (months)	27.18+15.91	27.13+17.64	0.9137
Drug-free period (months)	131.37+197.16	76.67+56.02	0.7288

diogenic syncope by the positive tilt test who refused or suspended the proposed treatment, Natale et al[34] observed that 64.8% of them showed recurrence of the symptoms within 3±1.5 years of follow-up, 28% presenting syncope. The remaining patients were able to abort the event when feeling the first prodromic symptoms, thus preventing the syncope episode. Most of the patients presented early recurrence within the first 5 months. Probably, the maintenance of the general dietetic and behavioral measures has influenced the evolution behavior of these patients. In addition, the knowledge of the breaking-out situations and the acknowledgement of the prodromic symptoms led them to protect themselves.

Different clinical variables have been evaluated as possible predictors of recurrence. The frequency and number of syncope episodes previously to the diagnosis are described as independent risk factors[25,26,30,31].

Sheldon et al[32] tried to identify those patients at high risk of recurrence after a positive test, among the NMS patients diagnosed by the tilt test. For such, they used the time to the first recurrence episode. The actuarial analysis of the event-free probability within the first and second years was 72% and 60%, respectively. The authors showed that the number of syncope and the duration of symptoms previously to the diagnosis were important predictors of the recurrence probability.

From those studies, the patients with NMS were classified into three subgroups. Those with history of more than six syncope episodes are considered as at higher recurrence risk; from three to six episodes, moderate risk, and less than three episodes, lower risk.

Patients selected in our study are considered as at moderate risk, with an average pre-test syncope incidence of three episodes/year. All were highly symptomatic, with commitment of the quality of life, reason why the specific treatment had been indicated. Among the clinical variables analyzed, the higher number of previous syncope was related to a higher probability of recurrence after therapy suppression, which corroborates the literature data. Females were also correlated to a higher probability of recurrence ($p=0.0131$), although other authors have not observed this[32,33].

The studies evaluating the role of tilt test in the clinical follow-up of syncope have conflicting results, hence its utility being still considered as controversial[32-34]. Sheldon et al observed that the unexplained syncope patients and those with typical history of neurocardiogenic syncope with positive or negative tilt test, showed similar clinical behavior, i.e., the same probability of recurrence during follow-up[32]. Brignole et al[35] suggested that after a positive test, there is a trend to decrease the symptom recurrence rate over time, regardless of the administration of placebo or tilt guided treatment. An explanation for this fact is perhaps the patient's learning of how to prevent syncope from the first prodromic symptoms and avoiding the breaking-out factors. In a previous study, Hachul et al[18] evidenced a significantly lower recurrence rate after therapy introduction, when a negative tilt was achieved in relation to those patients maintaining a positive test ($p<0.001$). Natale et al[34] evaluated the efficacy of different therapeutic strategies in neurocardiogenic syncope patients and observed that the recurrence was significantly lower in those patients at tilt test-guided therapy ($p<0.01$).

The tilt test result after treatment interruption was an independent predictor factor for recurrence risk in our study, especially within the first year. The time for first recurrence in patients with positive test was significantly lower than for those with negative test. Although literature has many controversial results in relation to tilt test usefulness in the therapeutic management of NMS, studies analyzing patients after therapy interruption are scarce. From our data, we observed that almost all patients with indication for specific therapy present recurrence after its interruption. To decide keeping them or not using medications, the tilt test should be considered as a criterion of risk evaluation.

Conclusions

The majority of the patients with NMS and indication of specific treatment present symptom recurrence over time after therapy supression. A TT carried out after treatment discontinuation can identify patients with higher risk of recurrence, specially in the first year of follow-up.

No potential conflict of interest relevant to this article was reported.

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