Introduction and objectives. Little information is available on the evolution of pediatric patients with vasovagal syncope. We therefore aimed to assess the medium-term clinical outcome of children evaluated by tilt testing for syncope of unknown origin.

Patients and method. Fifty-one children under 17 years of age who had undergone tilt testing were identified from a data base and studied prospectively. Kaplan-Meier and Cox regression analyses were performed to estimate syncope-free survival, its predictors, and the relative risks of several patient subgroups.

Results. Forty-seven (92%) of the children were followed for a mean 21 ± 9 months. The rate of recurrence of syncope was considerably lower than that estimated during history taking before the tilt test (19% vs. 47%; p < 0.01). Although the low rate made it difficult to identify predictors, several potential predictors emerged from the multivariate analysis. Only the history of more than one syncope before the tilt test (vs. isolated syncope) was found to have independent predictive value (p = 0.04). The cumulative probability of recurrence projected for a period of 38 months was 66.2% (SEM = 16.5%) for children with more than one syncope before testing vs. 0% for those who had experienced only one. No other events occurred.

Conclusions. The medium-term prognosis seems to be good for children with vasovagal syncope of unknown origin, given the low rate of recurrence, regardless of the results of tilt testing. The only predictor of recurrent syncope was pretest history, such that children with only one syncope before testing experience no recurrence and those with one or more episodes are estimated to have an increasingly higher likelihood of recurrence. These data may be useful for the recommending tilt testing and for planning therapy for children with vasovagal syncope.

Key words: Syncope. Childhood. Vasovagal syndrome. Tilt test.
INTRODUCTION

Data from the Framingham study indicate that 3% of men and 3.5% of women suffer a syncopal episode in the course of their lives. Many of these episodes must occur at early ages because the prevalence in childhood is around 15%. The majority of syncopal episodes in children or adults are of vasovagal origin, particularly when structural cardiac disease is absent.

In up to 70% of patients, syncope occurs as an isolated episode. On the other hand, if the manifestations are typical, the medical history suffices to identify the vasovagal origin of the condition. When both circumstances coincide, complementary tests or therapeutic action seem unnecessary. It should be enough to reassure the patient with regard to the nature of the condition and its good prognosis. Nevertheless, syncope can recur and even a single episode may involve alarming symptoms, such as convulsions or loss of sphincter control, or cause injuries that require confirmation of the diagnosis and an estimate of the possibilities of recurrence.

The tilt-table test has been proposed as a useful tool for diagnostic assessment. However, little is known about its capacity to predict new events, especially in pediatric patients. Consequently, the goal of our study was: a) to study the intermediate-term evolution of a cohort of 51 children referred for a tilt-table test for syncope of unknown origin, and b) to attempt to identify variables that reliably predict the possibility of recurrence of syncopal conditions.

PATIENTS AND METHOD

Study population

In a retrospective analysis of a prospective database of patients referred for the tilt-table test for suspected vasovagal syncope, we identified 51 patients under the age of 17 years. In every case we had the medical history, physical examination, ECG, chest radiograph, echocardiogram, 24-h Holter study, and neurological study, including an electroencephalogram and CT in the cases in which these examinations were indicated. The examinations cited failed to elicit information on the cause of syncope in any patient.

Before the tilt-table test was performed, the patient and family members were interviewed to determine how many syncopes had occurred, the frequency of syncope, premonitory symptoms, and the presence of relevant trauma (injuries requiring medical attention) and/or convulsions. In addition, a subjective estimate was made of the deterioration in quality of life originated by the condition using a qualitative 5-point scale. A pretest evaluation was made of the probability (high, medium or low) that the syncope was of vasovagal origin according to the subjective criterion of the cardiologist who made the test.

Protocol of tilt-table test

Patients were instructed to have only a liquid breakfast on the day of the test. A peripheral vein was cannulated, and then the patient was kept in supine position for 30 min in a quiet room. Blood pressure was controlled with an automated cuff system. Four ECG leads were monitored and recorded throughout the test. The baseline test was made by tilting the table 70° for 30 min or until syncope occurred. If the response was negative, a provocation test was carried out with a low-dose perfusion of isoproterenol adjusted for weight (0.02 mg/kg/min); once the heart rate stabilized, 70° tilting was repeated for 10 min or until positive signs appeared.

The test was considered positive when syncope or presyncope accompanied by hypotension (fall in systolic blood pressure below 80 mm Hg or at least 30 mm Hg) and/or bradycardia occurred (heart rate of less than 45 beats/min). Otherwise, the result was considered negative.

Follow-up

The decision to treat was made by a pediatric cardiologist who was advised to prescribe empirical therapy with beta-blockers if the previous syncopes had been recurrent and sufficiently frequent as to impair the quality of life, if a single syncopal episode had been accompanied by alarming symptoms (severe trauma and/or convulsions), or if presyncope was frequent. In no case was a cardiac pacemaker indicated. Follow-up visits were held in the pediatric cardiology outpatient clinic or conducted by telephone contact with family members.

Statistical analysis

All patient data were collected prospectively and consecutively, and entered into a database for later analysis using the SPSS for Windows statistical package. Syncopal recurrence was investigated by the comparison of subgroups defined by predictors using the odds ratio of an analysis of 2 binomial proportions. The time until a new syncopal episode occurred was analyzed using the Kaplan-Meier method, and the log rank test was used to compare the different curves. Comparisons with P<.05 were accepted as significant.

RESULTS

A mean follow-up of 21±9 months (range, 2-41 months) was completed in 47 (92%) of the 51 patients
who underwent tilt-table testing. The main baseline characteristics of the 47 patients followed-up are summarized in Table 1.

Nine patients (19%) had a syncopal recurrence, whereas the rest remained asymptomatic throughout the follow-up period. This recurrence rate contrasts with the pretest rate (47%, \( P = .01 \)). This explains why all the patients, except two, experienced a subjective improvement. In relation to the syncopal recurrence, three of the variables analyzed were found to be predictive of recurrence (Table 2): having more than one syncope as opposed to a single syncope before the test was made (\( P = .04 \)), suffering more than 6 versus fewer than 6 syncopes (\( P = .008 \)), and beta-blocker treatment (\( P = .04 \)). Evidently, the last variable was biased by therapeutic recommendations, and its significance disappeared when multivariate analysis was applied. None of the variables related to the tilt-table test was predictive of recurrence, whether the test result, the time to the appearance of positivity, or positivity at baseline or in response to isoproterenol provocation. The time from the last syncope to the tilt-table test was not a useful predictor either.

The application of the temporal function to the event of recurrence disclosed a significant difference (\( P = .05 \), log rank test) between the subgroups of a single syncope and more than one syncope (Figure 1). This probabilistic analysis estimated that after 38 months no patient in the single-syncope subgroup would have a recurrence, whereas 66.2% (MSE=16.5%) of the subgroup with more than one pretest syncope would have new syncopal episodes. It can be appreciated in Figure 1 that the curves do not begin to separate until 9 months of follow-up have passed.

**DISCUSSION**

The results of our study demonstrate that vasovagal syncope is a benign condition in children. There was no mortality and almost all the patients had a subjective sensation of improvement (95%). This was the case although the rate of therapeutic intervention

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**TABLA 1. Baseline characteristics of the population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>( N=47 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>11.5±2.7</td>
</tr>
<tr>
<td>(6-16, median 12)</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>20/27</td>
</tr>
<tr>
<td>Structural heart disease*</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Probability of vasovagal origin</td>
<td>31 (66%)</td>
</tr>
<tr>
<td>More than one syncope</td>
<td>22 (68%)</td>
</tr>
<tr>
<td>No. of synapses</td>
<td>5.6±14</td>
</tr>
<tr>
<td>(median 2)</td>
<td></td>
</tr>
<tr>
<td>Convulsions and/or trauma</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Positive tilt-table test</td>
<td>20 (42%)</td>
</tr>
<tr>
<td>Asystole during test</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Treatment with beta-blockers</td>
<td>12 (25%)</td>
</tr>
</tbody>
</table>

* A patient with a bicuspid aortic valve and another patient with a mitral prolapse and mild insufficiency.

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**TABLA 2. Variables predictive of syncopal recurrence**

<table>
<thead>
<tr>
<th>Reason for disparity</th>
<th>(95% \text{ CI} )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1.62 (0.35-7.45)</td>
<td>0.71</td>
</tr>
<tr>
<td>&gt;6 syncopal episodes</td>
<td>5.5 (2.02-14.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Impairment of quality of life</td>
<td>2.58 (0.57-11.70)</td>
<td>0.24</td>
</tr>
<tr>
<td>Low probability of vasovagal</td>
<td>1.04 (0.22-4.90)</td>
<td>1.00</td>
</tr>
<tr>
<td>syncope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 versus one syncope</td>
<td>12.53 (0.68-231.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Convulsions and/or trauma</td>
<td>3.43 (0.73-16.18)</td>
<td>0.19</td>
</tr>
<tr>
<td>Positive tilt-table test</td>
<td>1.10 (0.25-4.76)</td>
<td>1.00</td>
</tr>
<tr>
<td>Asystole during test</td>
<td>3.30 (0.62-17.62)</td>
<td>0.17</td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>5.12 (1.10-24.47)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
in our series was very low, no patient was treated by
cardiac pacing, and hardly one-fourth received beta-
blockers. On the other hand, only 9 patients (19%)
presented recurrence of syncope in the course of
follow-up. These good prognostic findings coincide
with those obtained in the adult population: 7%-30%
of recurrences in studies with a mean follow-up of up
to 31 months.17-22

The drastic reduction in the rate of recurrence
observed after the tilt-table test, which was not
attributable to therapeutic interventions, has been
reported in previous studies.23-27 It is thought that this
is due to a mixture of factors, such as the cyclical
nature of the syndrome, the reassurance of knowing
that the condition is benign, or training to adopt
positions that can prevent the progression of a
presyncopal episode to syncope. Another possibility is
that the observation time of our study was insufficient
to detect a higher recurrence rate. In fact, if the curves
in Figure 1 are examined, it is evident that up to 9
months they did not begin to separate, but from then
on the separation accelerated. Malik et al 28 studied the
temporal characteristics of recurrences after a positive
tilt-table test, concluding that recurrence was early
when it occurred, the mean time to the first recurrence
being 5.3±6.9 months. In the study by Natale et al 26
most of the recurrences appeared in the first 5 months,
and none after 16 months. In any case, the study by
Malik et al validated the usefulness of the time to the
first recurrence as a predictor of the frequency of
syncope. Therefore, although predicting the definitive
cure of the condition would be excessive and the long-
term appearance of syncope clearly cannot be
excluded, we think that it is still interesting to identify
cases of early recurrence, which should correspond
with the cases that are most symptomatic and
susceptible to benefit from a more exhaustive
diagnostic and therapeutic approach.

Whatever the case, the low rate of recurrence and
the small series make it difficult to find positive
predictors of syncopal recurrence within a Bayesian
case. Consequently, the markers of recurrence,
identified in studies of a predominantly adult
population have not been verified by our analysis. We
have discussed, for example, the absolute number of
syncopal episodes recorded in the pretest interview19,23
and the duration of the syncopal problem.23 In any
case, variables such as the response obtained with the
tilt-table test 19 or the appearance of asystole during the
test 20 have not served in these studies to predict future
syncopal episodes.

In our study, the only significant predictors were
the binomial distribution of single syncope versus
multiple synapses. When a temporal function was
applied to the analysis of the syncopal recurrence, the
estimated probabilities are very different in the single-
syncope versus recurrent syncope subgroups. This

finding could be rephrased: the patient who has had a
single syncope at the time of referral for tilt-table
testing has a very low probability of having another
syncopal episode. That is to say, single syncope is a
powerful negative predictor of recurrence. What
practical interest could this finding have? Children
with a low risk of recurrence, single syncope and,
perhaps, fewer than 6 syncope, can evolve favorably
without pharmacological treatment with the assurance
that serious events are rare and trauma secondary to
syncope is less frequent than in adults.29 This criterion
avoids exposing them to the possible secondary
effects of treatments whose effectiveness is doubtful.
There will always be time to reevaluate this attitude
in the case of recurrence. The relevance of these
findings is limited when analyzed in the context of
efficiency. The findings of this study suggest that
patients with a single syncope do not need to undergo
tilt-table testing, since no information about
recurrence is obtained from the results of this test,
including the appearance of asystole. If this guideline
were followed, we would have avoided 32% of tests,
those corresponding to patients with a single pretest
syncope. To be coherent, this recommendation should
also be followed in patients in which a single syncope
is accompanied by alarming symptoms, such as
convulsions and/or trauma. Nevertheless, in practice,
particularly when children are involved, the
environmental pressure is such that we are compelled
to perform the test, if for no other reason than for
purposes of reassurance, which facilitates the
management of the problem. In contrast, patients with
several preceding syncope have a significantly
higher probability of recurrence and the tilt-table test
is useful, in first place, to confirm the diagnosis, and
in second place, to identify the rare cases with severe,
persistent clinical manifestations in spite of
pharmacological treatment, in order to guide therapy
if permanent pacemaker implantation is contemplated.
The assumption is that only patients
with a cardioinhibitor component benefit from pacing,
which is the criterion used in studies that demonstrate
the benefit of pacemakers in adults.30,31

Limitations of the study

As we have mentioned, the main limitation of this
study resides in the small size of the sample; this
factor, along with the low rate of syncopal recurrence
observed during follow-up, makes it difficult to find
predictors of syncopal recurrence. For example, the
disparity between convulsions and/or trauma seems
considerably greater in the group that presented
syncopal recurrence (Table 1); however, it is not
significant (P=.19). This is due to: a) the low
recurrence rate, and b) the scant incidence of the
variable analyzed. A simple statistical calculation

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indicates that with a population of the same characteristics as the study population in terms of the recurrence rate and frequency of events, we need no fewer than 80 patients to obtain an acceptable level of significance. We have already mentioned that if the period of observation had been more prolonged, we probably would have obtained a higher rate of recurrence that would have facilitated the analysis. Another reservation is that we included in our study all the patients referred for tilt-table testing, not just those with positive test results, as has been done in other studies. Since the sensitivity of tilt-table testing is unknown, although attempts have been made to quantify the sensitivity, it seems more realistic to analyze the evolution of vasovagal syncope in relation to the test result. In fact, more than half of the syncopal recurrences in our series were observed in patients with a negative test result.

CONCLUSIONS

This study demonstrates that the vasovagal syndrome seems to have a benign course in pediatric patients, with a recurrence rate of only 19%, which is considerably lower than that estimated before tilt-table testing. The main finding was that syncopal recurrences did not begin until the ninth month of follow-up and exclusively affected patients with more than one syncope before carrying out the tilt-table test, an examination that has not been shown to have prognostic utility. This finding suggests that patients with only one pretest syncope do not need to undergo the tilt-table test nor do they require pharmacological treatment due to its extremely benign evolution.

REFERENCES


