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Minimal Vasovagal Dysautonomia in Patients with Rare or Unique Syncope

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Abstract

Introduction: It is common to find people sent to perform a Head Up Tilt Test (HUT) who suffered a single syncope, or syncopes that occur during certain periods and never appear again. We wonder how these people are different from those who have never had syncope. Methods: We found 300 patients who suffered only one (unique) or a maximum of 5 vasovagal syncopes during their life. And their HUT was positive for vasovagal dysautonomia. We compared them, with 120 healthy volunteers who have never had syncope. We try to explain how some constitutional predisposing factors act in these patients, and are associated with environmental triggers to precipitate the syncope. Results: We found differences between cases and controls in predisposing factors such as: heredity, joint hypermobility, baroreflex failure, venous compliance and some neurological diseases. Then an environmental factor acts as a trigger for syncope: prolonged standing, stress, pain and emotions, dehydration, use of certain drugs, abundant food. Conclusions: There are people with minimally expressed vasovagal dysautonomia who have an organic predisposition to present vasovagal syncopes (heredity, joint hypermobility, baroreflex failure, venous compliance, some neurological diseases, etc.). But this predisposition is not enough by itself to produce syncopes. One or more environmental factors must be added, acting as a trigger that would be the reason why these episodes are so infrequent.

Keywords

Dysautonomia, Unique Vasovagal Syncope, Head Up Tilt Test

1. Introduction

In our clinical practice performing Head Up Tilt Test (HUT) we found 300 patients, suffering only a single syncope or short periods with syncope that later disappear.

Our objective is to describe predisposing factors that we find in these persons that probably suffer from minimal dysautonomia.

1.1. Definition of the Group to Study

Between 2006 through 2021 we found 300 patients who consulted after having suffered a single syncope or a maximum of 5 episodes in their lifetime, in whom the positive HUT suggests that there was a hidden predisposing vasovagal dysautonomia.

Also shown are 120 healthy volunteers, who have not suffered from syncope, with an age and sex comparable to the patients

1.2. Ethical Clearance

Our study has been approved by the Militar Hospital's Ethics Committee, and has been carried out in accordance with the ethical standards established in the Declaration of Helsinki 1964. Patients and controls gave their informed consent before inclusion. Anova and logistic regression are used for statistical comparison and, depending on the sample size, a non-parametric test is used.

2. Material and Methods

2.1. Previous Study to Head Up Tilt Test and Inclusion Criteria

Our investigation included a retrospective data analysis of 1034 patients studied with HUT (60% women), carried out between 2006 and 2021. The average age of these patients was 30.5 years (range: 6 - 89 years).

In this persons we found 300 cases (29% of the patients examined in that period), which fulfilled the definition of the group to be studied

To rule out a cardiac or other cause, prior to the HUT, a careful medical history is taken, physical examination, evaluation by a cardiologist and some tests: electrocardiogram (12 leads), echocardiogram, heart rate 24 hours holter, and sometimes an electrophysiological study. If this previous study is negative, the patient is referred for our neurological evaluation and HUT.

One hundred and twenty volunteers of the same age and sex served as controls.

Subjects and controls were recruited from patients at the Santiago's Militar Hospital.

2.2. Exclusion Criteria

If a cardiac cause was found, the patient was not included. The same if the patients suffer from epilepsy or pseudosyncopes.

Patients whose HUT was negative were excluded, in order to study only those

patients with a higher probability of vasovagal dysautonomia.

3. Head Up Tilt Test Exam Conditions

Fasting patient (between 8 and 12 hours). Quiet room, with dim light at a temperature between 20˚C - 22˚C.

Exam is supervised by a neurologist, a cardiologist and a medical technologist. Cardiology staff install continuous ECG and HR monitoring.

A hemoglucotest is done before the exam.

Electrocardiographic monitoring and continuous measurement of blood pressure and heart rate is performed. In case of an emergency, medications, venous line, defibrillator and equipment for cardiopulmonary resuscitation are available.

4. Head Up Tilt Test Protocol

A record of heart rate (HR) and blood pressure (BP) and of symptoms reported by the patient is kept every 5 minutes. Any important incident is noted and recorded at any time. The sublingual nitroglycerin protocol is based on Del Rosso [1].

Time line: Initial questioning (15 minutes)/Monitoring installation (digital cuff to measure BP and continuous electrocardiogram) (10 minutes)/Basal HUT (horizontal) for 10 minutes/Passive HUT (standing at 70˚) 45 minutes/active HUT with 0.3 mg of sublingual trinitrin (without laying the patient down) for 10 minutes/Final recovery lying down (6 minutes) Total HUT: 55 minutes. Approximate total time: 90 minutes.

Carotid massage is performed on all patients over 60 years of age. Previous discard of murmur or carotid stenosis or stroke in the last 6 months. Five minutes on each side [2] [3] [4].

Tilt Test ends, if a "positive HUT" is obtained: This is if syncope (loss of consciousness) or presyncope occurs (dizziness, nausea, paleness, etc., announcing that syncope is imminent). Associated with low blood pressure (systolic BP < 70 mmHg) or low blood pressure plus bradycardia, or if intolerable patient discomfort occurs.

If there are no symptoms, HUT is terminated due to the end of the protocol.

In addition, sympathetic and parasympathetic function tests (Valsalva maneuver and deep breathing test) are performed in order to support or rule out failure in the baroreflexes.

The equipment consists of: Digital monitor (Ohmeda 2300 Finapres BP Monitor USA). Digital cuff placed on the index or middle finger to measure BP and HR continuously. Electric tilting table (Magnetic Manumed USA) and electrocardiogram monitor (Quinton Q4500 USA). The patient is fastened to the table with two velcro straps (knees and chest).

For the statistical comparison, Anova and logistic regression are used, and depending on the sample size, a non-parametric test is used.

5. Results

The age (at the moment of HUT) and sex of cases and controls can be seen in Table 1.

In Table 2 we can see the number of patients, number of syncopes and the time between the episodes.

Table 3 shows the result of the Tilt test in 300 cases.

All volunteers presented a negative HUT.

We found some factors that are linked to syncope in these patients. These are: heredity, joint hypermobility, venous congestion during HUT, food intake, drug use, emotional stress, and pain.

Joint hypermobility ("ligamentous hypermobility")

We found a very important prevalence (192/300) (64%) of joint hypermobility in our patients (score 5 or ≥ on the "Beighton Scale") [5] [6] [7].

113 (37.5%) of our patients had a family history of syncopes in first degree relatives, of whom 70% have joint hypermobility.

Forty-three percent (83 cases) of our hypermobile patients reported that syncope occurred or increased during a period of strong emotional stress, and then at the end of this period the syncope eased.

Of the healthy volunteers, only 2.5% ($p < 0.02$) had a joint hypermobility score 5 or ≥ on the "Beighton Scale".

Table 1. Average age and sex of cases and controls.

	Cases			Controls		
	Male	Female	Total	Male	Female	Total
% patients	44% (n = 132)	56% (n = 168)	300	45% (n = 54)	55% (n = 66)	120
Average age (years)	33.7	33.6	33.4	37.6	36.5	37.0

Table 2. Patients with syncope. Number of patients, number of syncopes and time between episodes.

N° of Syncopes	1	2	3	4	5	Total
N° of cases	102	72	57	49	20	300
Range of time	Unique	2 months to 20 years	3 months to 10 years	2 months to 30 years	6 months to 15 years	2 months to 30 years
Average years between episodes	-	5.3 years	4.7 years	5.4 years	6.6 years	5.5 years

Table 3. Tilt table test results in 300 cases.

HUT Results	N	%
Vasodepresor syncope	144	48%
Orthostatic hypotension	72	24%
Mixed syncope	66	22%
Cardioinhibitory	18	6%
Total	300	100%

Orthostatic intolerance due to prolonged standing

22% of patients (66 cases) reported that their symptoms were precipitated by 20 to 30 minutes of standing, thus they avoided prolonged standing such as queuing or ceremonies of any kind.

In 80% of these 66 patients prolonged standing during HUT induced syncope or severe orthostatic hypotension. This forced us to return the patient in recumbent position.

In these patients we found associated factors such as heredity (72%), joint hypermobility (76%) and increased venous pooling in standing position (82%).

In healthy controls, prolonged standing causes discomfort in the legs and sometimes plantar pain. But dizziness or syncope did not occur.

Fear, emotional stress and pain

It is common for patients examined after one or several syncopes to indicate that fear, pain or emotional stress coincide with the period of their syncope or lipothymia. And without the presence of these factors, syncope does not occur. [8] [9] [10] [11]. The frequency of these associated emotional factors is in our cases (185/300) = 61.5%. After the stress period is over, the syncopes disappear.

Of these patients, 43% were hypermobile, 25% had a family history of syncope, and 47% had large venous pooling in the lower extremities.

Of the healthy volunteers, 22 (18%) recalled having gone through intense periods of emotional stress during the last year. This period manifests in insomnia, headache, irritability or discouragement but not with the presence of syncopes or lipothymia ($p < 0.02$).

Regarding emotion or pain as syncope triggers, we found different types of patients: Some of them with sudden pain or emotions (for example, a hit, getting vaccinated or fear), and others with subacute emotions installed for several weeks (for example work or academic stress) and others with both conditions (n: 22 cases).

1) Sudden emotion or pain: 119 cases

a) Acute pain; b) Bleeding; c) Acute fear; d) Taking a blood sample or injections.

2) Subacute distress, emotion or stress overload: 44 cases

a) Concerns (financial or family stress); b) Work or study overload; c) Loss of a relative or divorce; d) Personal diseases.

In **Table 4** we see types of stressful or emotional factors acute and subacute associated with syncope.

Heredity

A family history of syncopes in first degree relatives of syncope is frequent [12] [13] [14] [15].

In 113 of our patients we found a history of syncope in first degree relatives (37.5% frequency).

In these patients, we found an association between heredity with emotional factors (pain, fear or stress) as a trigger for syncope (29/113): 26%.

Table 4. Types of stressful or emotional factors acute and subacute associated with syncope.

Acute event (n: 119)	Female (n)	Male (n)	Age of onset	Total (n)
Sudden fear	11	4	15 - 18	15
Hit or Pain	13	22	12 - 20	35
Blood sample or Injection	45	24	12 - 18	69
Subacute event (n: 44)	**Female (n)**	**Male (n)**	**Age of onset**	**Total (n)**
Work/Study overload	28	7	17 - 22	35
Loss of a relative or divorce	2	5	35 - 51	7
Personal illnesses	0	2	48 - 52	2

Of the healthy volunteers, only 0.8% ($p < 0.02$) recalled having had a family member with syncope.

Venous congestion ("pooling") in the lower extremities due to prolonged standing

We observed a relationship between the accumulation of "venous pool" in the passive phase of HUT and syncope. Venous congestion was measured by visual observation of the color and congestion in lower extremities and feet with a score ranging from 1 to 5.

1 = nothing (little or no change in color of feet), 2 = mild (pinkish feet), 3 = moderate (reddish feet), 4 = severe (dark reddish feet) and 5 = very severe (acrocyanosis and purple feet).

216 of 300 patients (72%), had, severe or very severe (score 4 or 5) venous congestion during passive HUT. From these 140 patients (65%) presented syncope or lipothymia during HUT. In contrast, only 28 patients with no venous congestion or only in a mild degree (score 1 or 2), had a positive HUT (9%) ($p \leq 0.02$).

Venous pooling found in our patients was closely linked to orthostatic intolerance (76%), prolonged standing (83%), ligamentous hypermobility (68%), postprandial syncope (78%) and a hereditary history of syncope (58%).

In the 120 healthy controls we found only 18 patients (15%) with significant venous congestion (score 4 or 5) ($p < 0.02$). In the rest (85%) the venous congestion was moderate or little.

Syncope during military standing formation

Thirty-three of our patients (11%) consulted for syncope during prolonged standing in a military formation (45 - 60 minutes). All were under 25 years of age (x: 22.5). 70% were hypermobile (≥5 Beighton scale), 66% had a family history of syncope and 69% had severe or very severe venous congestion in the lower extremities during the passive HUT.

None of the healthy controls, had syncopes during military standing formation ($p < 0.02$).

Post-prandial syncope, heavy food, or gastric discomfort

Twenty-six patients suffered from postprandial syncope (8.6%). Their syncopes were not related to hypermobility, heredity or emotional stress. Their age was on average older than most of the other patients (age X: 64 years). Their venous congestion score was 4 - 5 on our visual scale.

These patients suffered from diseases such as: supine hypertension in 84%, orthostatic hypotension in 70%, diabetes in 38%, hypercholesterolemia in 27%, obstructive apnea in 11.5%, autonomic cardiovascular neuropathy in 19%, Parkinson's Disease in 6%, and multiple systemic atrophy in 1%.

Three patients started with post-prandial syncope after bariatric surgery and abdominal distension. Phenomenon that is known, but not yet be well explained [16].

None of the healthy controls suffered from postprandial syncopes ($p < 0.02$).

Use of prescription drug

In 10% of our cases (30/300), the effect of drugs was considered essential for the occurrence of syncope. These were mostly medications introduced before syncope started, or recently increased doses. Its subsequent removal or reduction resulted in relief of fainting.

The drugs alone or in combination, most associated with syncope due to orthostatic hypotension were: atenolol, carvedilol, valsartan, losartan, enalapril. Also some antidepressants with action in the CNS: venlafaxine, trazodone, sertraline or amitriptyline combined with each other or with hypotensive drugs.

The associated factors that we found linked with the drugs mentioned above in patients with syncope were: venous pooling in prolonged standing 85%, age ≥ 60 years 80%, orthostatic hypotension 50%, cardiovascular autonomic neuropathy 10% and postprandial syncope 6%. There were no cases associated to: heredity, joint hypermobility or emotional stress.

Twelve of the healthy controls (10%), consumed hypotensive drugs, but none suffered from syncopes ($p < 0.02$).

Dehydration and fasting

This combination occurred in 29 patients (9.6%) during a military campaign, with great environmental heat, under fasting conditions, without drinking fluids for 12 hours. It was the only syncope in their life. All cases had ≥5 in Beighton's scale of hypermobility. Twenty of them had a family history of vasovagal syncope.

Four of the healthy (militar staff) controls (3.3%) campaigned, fasted, without drinking fluids for 12 hours, but none fainted ($p < 0.02$).

Central and peripheral nervous system diseases

Four patients were type 2 diabetic with more of 35 years of evolution with severe autonomic and distal diabetic neuropathy. All four are consulted after one single syncope (age X: 79 years).

Other 3 patients had Parkinson's disease and orthostatic intolerance. They consulted after having four or five syncopal episodes (age X: 77 years).

In these 7 patients, syncope in HUT was preceded by severe orthostatic hypo-

tension.

None of these 7 patients was hypermobile, nor did they have relatives with syncope.

In 3 of them certain hypotensive agents were suspected as adjuvants of syncope: enalapril alone or in combination with diuretics, trazodone or amlodipine, losartan alone or in combination with amlodipine or atenolol or with diuretics.

None of the healthy controls suffered from central or peripheral neurological diseases.

A summary of the predisposing factors to present syncope can be seen in **Table 5**.

6. Discussion

Heredity

Family history of syncope is described in 19% - 90% of first-degree relatives of patients with syncope [12] [13] [14] [15]. In our sample, this relationship was 37.5%.

The existence of vasovagal syncope shows a much higher concordance in monozygotic twins than in dizygotic twins [15]. So heredity is clearly an organic predisposition to syncope. [12] [13] [14]. The association between heredity and syncope in our sample is remarkably clear. So for us having first degree relatives with vasovagal syncope is an important risk factor for fainting when an environmental cause is added.

Hypermobility and venous pooling in lower extremities

Hypermobile people have a higher proportion of type III collagen, which is more elastic. Their veins accumulate more venous pooling when standing up [17] [18]. Giving the conditions to trigger a syncope by systemic hypotension and cerebral circulatory deficit [5] [17] [18].

Table 5. Frequency of factors predisposing to syncope in patients versus controls.

Predisposing factors	Patients		Controls	
Heredity	n: 113	37.5%	n: 1	0.8%
Joint hypermobility	n: 192	64%	n: 3	2.5%
Severe venous pooling	n: 216	64%	n: 18	15%
Emotional stress and pain	n: 185	61.5%	n: 22	18%
Drug treatment	n: 30	10%	n: 12	10%
Postprandial syncope	n: 26	8.6%	n: 0	0%
Fasting/ Dehydration	n: 29	9.6%	n: 4	3.3%
Neurological diseases	n: 7	2.3%	n: 0	0%
Prolonged standing	n: 18	6.0%	n: 0	0%
Military standing formation	n: 33	11%	n: 0	0%

We observed an increased venous pooling linked to orthostatic intolerance, prolonged standing, joint hypermobility, postprandial syncope and a hereditary history of syncope. Of our patients with severe or very severe venous congestion (grade 4 or 5), 63% had an intense degree of joint hypermobility ≥ 5 ($p \leq 0.02$).

The presence of joint hypermobility and the occurrence of lipothymia or vasovagal syncope is clearly linked [5] [6] [7], and even with POTS (postural orthostatic tachycardia syndrome) [5] [19] [20] [21].

Prolonged standing

Standing for long time causes blood retention in the veins of the abdomen, pelvis and lower extremities thus producing a decrease in venous return and orthostatic intolerance [16] and this is worse in hypermobile people.

Venous pooling was very clear in our patients during prolonged military standing formation or those who participate in standing ceremonies or queuing. [16].

Some articles support the use of compression stockings to reduce or eliminate venous congestion of the lower extremities [17] [18].

Emotional Stress, pain and fear

Fear, pain, stress and emotion have always been associated with vagal syncope [9] [11].

A higher frequency of recurrent vagal syncope has been found in depression, panic attacks, emotional stress, generalized anxiety and somatization disorders [8] [9] [10] [11].

Syncope improves, as the emotional state improves, or worsens when the opposite occurs [8].

The presence of pain, emotion, or fear as a trigger for syncope in our patients was associated with factors such as joint hyperlaxity, a family history of syncope and severe venous pooling in the lower extremities.

Post-prandial syncope, heavy food, or gastric discomfort

Failure of the baroreflexes is capable of producing hypotension and postprandial syncope. This is most commonly seen in older adults, parkinsonians, diabetics, hypertensive, and dialysis patients [22] [23] [24] [25].

In our experience these patients were not related to hypermobility, heredity or emotional stress. Their age was older than 60 years old and their venous standing congestion score was high (4 - 5 on our visual scale).

Syncope in them was mainly associated with orthostatic hypotension (87% late hypotension vs 13% early) and of course associated to prolonged standing (82%).

These patients suffered from infrequent diseases in other syncopal patients: Supine hypertension, orthostatic hypotension, Diabetes mellitus, hypercholesterolemia, obstructive apnea, autonomic cardiovascular neuropathy, Parkinson's Disease, and multiple systemic atrophy [23] [24] [25] [26].

Postprandial orthostatic hypotension occurs even in patients being treated for arterial supine hypertension [27] [28].

Syncope during military standing formation and **excessive venous pooling in the lower extremities**

Patients that consulted for syncope during prolonged standing military formation were mainly hypermobile, had a family history of syncope and had severe or very severe venous congestion in the lower extremities during the passive HUT.

Excessive venous pooling in prolonged standing is closely linked to orthostatic intolerance, joint hypermobility, and hereditary history of syncope [29] [30].

Use of prescription medications

Medications such as antihypertensive, diuretics, nitrates, beta-blockers, antidepressants, antipsychotics can predispose to the appearance of syncopes. This is worse in older adults, this group present more frequently alterations in the baroreflexes [31] [32].

We observe that the hypotensive action of these drugs in our study is aggravated by factors such as: venous pooling in long standing position, age ≥ 60 years, SNC diseases (ex. Parkinson), peripheral neuropathy, cardiovascular or diabetic autonomic neuropathy, cardiovascular diseases, postprandial hypotension and patients with polypharmacy [24] [32].

Fasting and dehydration

In certain persons fasting and hypoglycemia can be added to hypotension in the production of vagal syncope [33] [34].

In young women, a greater sensitivity to insulin has been seen. Their fasting glycemia tends to be lower than in controls, and they more frequently have a positive vasovagal reaction and even a positive HUT if they are fasting. [33] [34].

All these patients (n: 29) were hypermobile and 20 of them had a family history of vasovagal syncope.

Chronic diseases of CNS o PNS

Chronic diseases that affect circulatory regulation in the central and/or peripheral nervous system such as Parkinson's, Multiple Systemic Atrophy (MSA) and Diabetes mellitus, damage severely the autonomic baroreflexes and it is very likely that these patients will present many syncopes and falls during their life [35] [36] [37] [38].

In these patients, during HUT syncope was preceded by severe orthostatic hypotension (early or late hypotension). They were not hypermobile patients, nor did they have a family history of syncope. In them, the frequent use of hypotensive drugs is observed, as adjuvants of the syncopal picture (43%).

7. Study Limitations

First: It is difficult to obtain statistically valid conclusions due to the small number of patients studied in our sample. We understand that a greater sample is necessary in the future.

Second: We depend on the good memory of the patients or their relatives to recall their first syncopal episode or the total number of syncopes. In some cases,

the patient, after a second interrogation, remembers having suffered episodes during childhood or adolescence.

Third: Altough an exhaustive interrogation and pre-HUT exams, it is not always possible to completely rule out causes other than vagal syncope, such as drowsiness, vertigo, orthostatic dizziness or accidental falls.

Fourth: Despite follow-up and complementary examinations, there were 4 patients (1.3%), in whom we find only one factor that made them prone to syncope. In these four cases, syncope occurred only once. Therefore, it is difficult for us to attribute their case to a minimal dysautonomia or perhaps it was just a casual and unique syncope, unrelated to a dysautonomic propensity.

Fifth: Our visual scale, used to assess venous congestion of the lower extremities, is not yet internationally validated. It was our creation, documented with photos and statistically closely related [29] [30] to prolonged standing and joint hypermobility, but not yet validated.

8. Summary

People who suffer a single or very occasionally syncope during their life have a constitutional/organic predisposition to have a vagal syncope.

But syncopes do not occur unless an environmental factor appears (potentially manageable) unbalancing the circulatory balance. So these patients lead a normal life for many years, and their syncope occurs very infrequently (minimal dysautonomia).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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