

Current diagnosis and management of children with vasovagal syncope

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Background: Vasovagal syncope (VVS) is the most common type of syncope and a wide variety of stimuli can trigger this reflex. The morbidity is high in children with VVS. The aim of this review is to describe the diagnosis and treatment of children with VVS.

Data sources: Related articles in PUBMED and CNKI in the last decade were reviewed. The data on the diagnosis and management of VVS were extracted and analyzed.

Results: The diagnosis of children with VVS includes basic method (inquiring history of syncope and physical examination), head-up tilt table test (baseline head-up tilt test, sublingual nitroglycerin tilt test and isoproterenol head-up tilt test), and standing test. The therapy includes education, behavior modification, training, standing training, oral fluid therapy, pharmacological treatment (beta blockers, fludrocortisone, alpha agonists, selective serotonin re-uptake inhibitors and captopril), and permanent use of pacemaker.

Conclusions: Basic method (inquiring history of syncope and physical examination) is most important. Sublingual nitroglycerin tilt test is recommended in the diagnosis of VVS. Education, behavior modification, training, standing training, and oral fluid therapy are effective in preventing VVS, but the effect of all medicines needs to be further investigated.

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Introduction

Syncope is defined as the abrupt and transient loss of consciousness associated with loss of postural tone, typically followed by a rapid recovery. It is actually the decrease of brain blood flow for the moment. The reported morbidity is 15% in children aged under 18 years.^[1] A variety of conditions can cause syncope, but the most common cause is vasovagal syncope (VVS), which accounts for 80% in all cases of unexplained syncope (UPS). VVS is a benign condition characterized by a self-limited episode of systemic hypotension (less than 20 seconds) without nervous system signs. A wide variety of stimuli can trigger this reflex and alternatively it is called neurocardiogenic syncope.^[2] This article aims to provide an overview of the diagnosis and management of VVS on the basis of current evidence and our experience in this field.

Diagnosis

Basic methods

A detailed history of syncope and physical examination can offer many important clues for the diagnosis. The history should include whether there are prodromes such as lightheadedness, fatigue, pallor, diaphoresis, palpitation, chest distress, headache, tachypnea, stomachache, vomiting, blurred vision, blackout, vertigo, nausea, fever, numbness, and cyanosis, and whether there are motivations such as prolonged standing, orthostatic change, emotional upset, sweltering environment, fatigue, defecation, etc. Since physical examinations are often unfruitful, a stepwise approach is necessary for determining the diagnosis, such as 12-lead electrocardiography (ECG), 24-hour Holter monitoring, echocardiography, exercise tests, cranial computed tomography (CT), electroencephalography (EEG), and tests of myocardial enzyme, blood glucose and electrolytes.^[3] Boehm et al^[4] thought that if a history of syncope caused by exercise was elicited, this was unlikely to be VVS. But Vizmanos Lamotte et al^[5] reported a patient with exercise-induced syncope, whose results of cardiac and

neurologic tests were negative. The tilt table test (TTT) with pharmacological challenge with isoproterenol infusion induced arterial hypotension and presyncope, and a diagnosis of neurally-mediated syncope was made. After initiating beta-blocker treatment, the patient was asymptomatic during a follow-up of 10 months. In addition, Kouakam et al^[6] found that the risk of recurrence in children and adolescents with a history of syncope was not correlated to the tilt test result or prophylactic treatment. However, a number of syncope attacks were predictive. Similarly, Diaz et al^[7] showed that the only predictor of recurrent syncope was a pre-test history. Children with only one syncope before test experienced no recurrence and those with one or more episodes were estimated to have an increasingly higher recurrence rate.

TTT

In 1986, TTT was found effective in detecting autonomic tone abnormalities. At present, head-up tilt-table test (HUTT) has been a gold standard for evaluating patients with syncope. Udani et al^[8] reported that HUTT was highly sensitive in the diagnosis of VVS in children or adolescents and it was relatively safe and easy to perform. Unprovoked HUTT in children was reproducible when repeated on different days, and the results were comparable to those in adults.^[9] On the contrary, a few scholars held that HUTT had high false-negative and false-positive rates and should not be used to identify patients with VVS.^[10] In the past two decades, TTT has been improving, although not perfect. The standardized protocol for TTT may contribute to its efficacy and comparability.

Laboratory environment, judgement standard and response type

TTT should be performed in a quiet room with lights slightly dimmed and temperature comfortable so as to avoid any interference and reduce anxiety of the patient. Resuscitation equipments should be available such as first-aid medicine, oxygen, defibrillator, etc. Tilt tables should be equipped with footboard supports. Experienced nurses, technicians and physicians should be present during the test.

Positive result is considered if the patient has a significant decrease in blood pressure (BP) (<80/50 mmHg or at least a 25% drop of mean blood pressure over basal levels) and/or heart rate (HR) (<50 beat/min, among them HR<75 beat/min between 4 and 6 years, HR<65 beat/min between 7 and 8 years, HR<60 beat/min over 8 years), sinus arrest (>3 seconds) or junctional rhythm along with the development of unusual symptoms. The result is negative when these

signs and symptoms are absent.

On the basis of HR and BP, the response is classified into three types: vasodepressor response (BP falls markedly, accompanying with an HR increase), cardio-inhibitory response (HR falls markedly without a BP decrease), and mixed response (both HR and BP fall markedly).

Baseline head-up tilt test (BHUT)

Stop using any cardiovascular active medicine for over five half-life periods and any diets or drinks such as coffee, which may affect the autonomic nervous system. With no flexion of ankle joint and knee joint, the patient steps upon footboard supports and is fixed on test table by a band after an 8-hour fasting. After a 10-minute pre-test rest, the head of the table is tilted upward to an angle of 60 to 80 degrees (children 60 degree) while hemodynamic and electrocardiographic monitoring is performed. During the test, the patient should be tilted to a desired angle smoothly and rapidly, and possibly change quickly to a supine position (<15 seconds). HR is monitored continuously with a standard ECG monitor and BP is monitored with a standard sphygmomanometer intermittently at a 5-minute interval in addition to monitoring of clinical symptoms. The test lasts for 45 minutes unless hemodynamic collapse occurs in advance.

In this study, the test had a sensitivity of 37%-76% and a specificity of 80%-100%. It was of more value in excluding VVS than diagnosing VVS.^[11-15] Positive responses appeared after tilting from 22.4±13.5 to 24.7±12.9 minutes. Vasodepression response was the most common type, accounting for 70.0%-80.4%.^[16,17]

Sublingual nitroglycerin tilt test (SNHUT)

Not in a supine position, the patient with negative response in BHUT uses nitroglycerin sublingually 4-6 µg/kg each time (maximum 300 µg). HR and BP are monitored every one minute. As soon as positive response appears, the patient should be returned quickly to a supine position. The result is deemed negative without hemodynamic collapse and unusual symptoms during a 20-minute period.

Reports showed that SNHUT improved the positive response rate from 62.1% to 80.0% in pediatric patients,^[16,17] and the time to syncope attack was reduced. Dindar et al^[18] reported that SNHUT had a sensitivity of 77.5% and a specificity of 91.6%. Positive response after sublingual use of nitroglycerin increased from 5.5±3.1 to 5.9±2.9 minutes.^[14,15] Sublingual use of nitroglycerin in children was effective and objective in diagnosing VVS.

Isoproterenol head-up tilt test (ISOHUT)

There are single-stage ISOHUT and multi-stage ISOHUT. In single-stage ISOHUT, the patient with a negative response to BHUT is given intravenous isoproterenol at a dose of 0.05 µg/kg per minute in a supine position. When HR is stably increased (10% over the basal level), the patient is tilted again, observed for 10 minutes or till unusual symptoms appear. Multi-stage ISOHUT is similar to single-stage ISOHUT in the beginning. Isoproterenol at an initial dose of 0.02-0.04 µg/kg per minute is administered. If there is no positive response, isoproterenol is administered at a dose of 0.04-0.06 µg/kg per minute after 10 minutes. The above procedures and observation are repeated until isoproterenol is given at a dose of 0.06-0.08 µg/kg per minute.

Alehan et al^[19] evaluated 25 patients aged 8-15 years (median 11.8±2.1 years) after multi-stage ISOHUT. Compared to BHUT, the sensitivity and specificity of multi-stage ISOHUT were increased from 48.5% to 76.6% and from 86.7% to 93.4%, respectively. In 111 patients with a history of syncope (median 55±20 years), Shen et al^[20] found that 56% had a positive vasovagal response during the single-stage ISOHUT and 32% during the passive tilt table test. The mean procedural times of the study population were 11.7±3.6 minutes and 36.9±13.3 minutes for isoproterenol and passive tilt table test, respectively. Scholars found that multi-stage ISOHUT had a higher sensitivity of 75.0%-83.6% and a lower specificity of 66.7%-90.0% than BHUT.^[19-22] Despite isoproterenol can increase the sensitivity of tilt test, its venous cannulation may influence the stability of the automatic nervous system with more side-effects. Therefore it is difficult to be used in pediatric patients.

Standing test

Standing test is a peculiar form of the tilt table test at an inclination of 90°. Matsushima et al^[23] examined children and adolescents with orthostatic symptoms by two orthostatic tests, active standing test and head-up tilt test, and found that the standing test caused cardiac sympathetic activation associated with an initial pressure drop, and was more prone to inducing syncope with increased heart rate in some patients. Because standing is a daily postural motion, they concluded that standing test is potentially effective as HUTT for the diagnosis of syncope; but it might lead to a sensation of inclination and something uncomfortable for the patient.

Therapy**Education and behavior modification and training****Education**

The patient should be assured of the benign nature of VVS, but sometimes it may lead to injury to the body.

The patient is taught to recognize early symptoms of the disease so as to take preventive measures. Other effective measures include prevention of dehydration and prolonged standing, stay in warm environment, etc.

Behavior modification

Physical maneuvers should be taken when early symptoms of VVS appear. The simplest counter-manuever so far is assumption of a supine posture. The legs may be elevated to increase the venous return to the heart. Sitting and squatting may also be used. These counter-manuevers decrease the pooling of venous blood in the lower extremities and abdomen, while increasing the peripheral arterial resistance. The resultant increase of venous return to the heart, cardiac output, blood pressure, and cerebral perfusion leads to the elimination of presyncope. The combination of leg crossing and tension of the thigh and abdominal musculature is highly effective in preventing reflex syncope in young patients.

Standing training

In highly motivated patients with recurrent symptoms, progressively prolonged periods of enforced upright posture or tilt training might reduce the recurrence of VVS by lowering vascular compliance in the compartments most responsible for venous pooling.^[24] Raising the head of the bed during sleep (>10°) contributes to the improvement of the symptoms.

Respiratory training

Paced breathing preventing VVS induced by HUTT was observed in 10 patients (median 18.4±5.1 years) as reported by Jauregui-Renaud et al.^[25] They suggested that respiratory training is useful to prevent VVS.

Oral fluid therapy

As a primary intervention, increased intake of fluid and salt is an effective treatment of VVS. Oral fluid therapy may increase plasma volume and avoid the hypercontractile state of the ventricle in the head-up tilt test or the so-called "empty" effect induced by reduced cardiac filling. Thus the parasympathetic output is not increased to prevent the onset of syncope. A study showed that patients had a high positive but a low negative predictive value of response to oral fluid therapy.^[26] The patients with a positive response to oral fluid-therapy were given 250-500 ml of normal saline after recovery (about 10 minutes) and rested in a supine position for 20 minutes. Again they were subjected to HUTT and 78.9% of them showed a negative response.^[15]

Pharmacological treatment**Beta blockers**

Beta-adrenergic receptor antagonists prevent the stimulation of left ventricular mechanoreceptors and the increase of circulating epinephrine. Previous studies provided positive evidence for the benefits of β -blockade in treatment of VVS; but randomized controlled trials in the recent 5 years reported no difference between placebo and β -blockade in the treatment of VVS.^[1,27,28] The side-effects of β -blockade such as reduction of heart rate and block of atrioventricular conduction might aggravate syncope.^[29] Flevari et al^[27] conducted a prospective, randomized, crossover study to assess the relative therapeutic efficacy of propranolol, nadolol and placebo in 30 patients with VVS and a positive head-up tilt test. Therapy with each drug lasted for three months. The results showed that propranolol, nadolol and placebo were equally effective in the treatment of VVS, as demonstrated by a reduction in the recurrence of syncope and presyncope, as well as an improvement in the patients' well-being. Madrid et al^[28] performed a prospective, randomized, double-blind, placebo-controlled study in 50 patients with recurrent VVS. The primary end point of the study was set at the time to the first recurrence of syncope. They found that the recurrence of VVS in highly symptomatic patients treated with atenolol was similar to that of patients treated with placebo after follow-up for one year. Twenty-nine patients with VVS (6-16 years) took metoprolol 12.5 mg every time, twice a day for 1 week to 3 months. After the follow-up of 3 months, 66.7% of these patients had a negative response to the head-up tilt test. Without serious side-effects, syncope attacks were significantly reduced. Therefore, Jian et al^[30] thought that metoprolol was effective and safe in children with VVS.

Fludrocortisone

Fludrocortisone, a synthetic mineralocorticoid, acts on the distal tubules of the kidney to retain sodium and hence expands blood volume and prevents relative central hypovolemia. Apart from increasing pressure receptor sensitivity to circulating catecholamine and vessel reactivity to vaso-exciting material, fludrocortisone reduces the activities of the parasympathetic nerve and plays a part in the treatment of VVS. Salim et al^[31] studied 33 children (median 13.9 \pm 2.5 years) with syncope, who were randomized in a double-blind fashion to receive either fludrocortisone 0.1 mg/d and salt 1 g/d or placebo two capsules per day for one year. After follow-up for one year, symptoms recurred in 55.6% children on fludrocortisone and salt and in 35.7% children on placebo. Children on placebo had no symptoms until they discontinued their study medications, which raised the potential effect of a significant placebo with pharmacologic therapy.

Alpha agonists

These drugs exert their effect peripherally by increasing vascular resistance and decreasing venous pool. Midodrine is a representative in this drug group and its potential side-effects include skin rash, paresthesia, urinary retention, supine hypertension, etc. Perez-Lugones et al^[32] randomly allocated 61 patients with severe VVS to treatment either with midodrine or fluid, salt tablets, and counseling. Midodrine was given at a starting dose of 5 mg three times a day and increased to a dose of 15 mg three times a day when required. The agent was given in the daytime every 6 hours. A 6-month follow-up revealed that 81% midodrine-treated patients and 13% fluid-therapy patients remained asymptomatic. Midodrine appeared to be significantly effective in patients with VVS. To prevent recurrence of symptoms, the dose of treatment was adjusted. Kaufmann et al^[33] investigated 12 patients with recurrence of neurally mediated syncope, which was reproduced during the head-up tilt test. The patients were randomized to receive midodrine (5 mg) or placebo on day 1 and the opposite on day 3. One hour after administration of drug or placebo, the patients underwent head-up tilt test again. The responses to head-up tilt were significantly different on the midodrine and placebo day. On the placebo day, 67% of the patients suffered from syncope, whereas only 17% developed syncope on the midodrine day. These results indicated that midodrine significantly improved orthostatic tolerance during the head-up tilt test in patients with recurrent VVS.

Selective serotonin re-uptake inhibitors

Serotonin leads to bradycardia and pressure decrease mediated by the parasympathetic nerve. Paroxetine and sertraline have been used in patients with VVS. In a randomized placebo-controlled study on 68 adult patients with refractory VVS, Di Girolamo et al^[34] found a negative tilt test in 61.8% of the patients on paroxetine and 38.2% of placebo-treated controls after one month of treatment. Paroxetine was found to significantly improve the symptoms of patients with VVS and was well tolerated by the patients. Lenk et al^[35] studied 15 patients (median 12.9 \pm 2 years) with VVS, who were given 50 mg oral sertraline hydrochloride daily. Intolerance to the drug was seen in 3 patients, and 2 patients had syncopal episodes during the therapy. HUTT was then repeated in 10 patients, of whom 6 showed negative results. They concluded that sertraline hydrochloride may be useful in preventing recurrent VVS, but clinical studies are essential before this treatment is recommended since serious asystole can develop.

Captopril

Captopril is one of angiotensin-converting-enzyme

inhibitors. It can prevent production of angiotensin II and reduce stimulation to angiotensin II receptor so that plasma catecholamine secretion is inhibited. Captopril can be effectively used in the treatment of VVS via the blockade of the Bezold-Jarisch reflex.^[36]

Permanent pacemaker therapy

A few patients with VVS require pacing when they were associated with gradually extended asystoles or recurrent asystoles.^[24] Permanent pacemaker implantation is mainly applied to cardio-inhibitory type patients. To determine whether permanent cardiac pacing could prevent syncope in children with frequent severe VVS, and whether dual chamber pacing was superior to single chamber ventricular pacing, Mcleod et al^[37] conducted a double-blind experiment in 12 children aged 2-14 years (median 2.8 years) and thought that permanent pacing was an effective treatment for children with severe VVS. Single chamber ventricular pacing was as effective as dual chamber pacing in preventing syncope, but the latter was advantageous in preventing overall symptoms. This finding is consistent with that of some studies in adults, which advocated dual chamber pacing as the most effective pacing program. Owing to the small size of the pediatric patient, there is an increased risk of complications at the time of implant and problems related to future growth. Hence single chamber ventricular pacing is suitable for a younger child. Since older children are aware of the unpleasant prodromes or more troubles from pacemaker syndrome, a dual chamber pacemaker is preferable.

Current problems

Despite lots of researches into VVS in children, its pathogenesis remains obscure. The head-up tilt test fails to form uniform standards and no large-sample, randomized, controlled study has been undertaken to evaluate the best treatment option for VVS. Further multi-center cooperative studies are needed to be carried out.

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