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Research Article

Progress in the Diagnosis and Treatment of Syncope in Children and Adolescents

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Abstract

Syncope is defined as a transient, self-limiting loss of consciousness and postural tone, and recovery is spontaneous, rapid, timely, and complete without any neurological sequelae [1]. This paper reviews a series of research progress made by scholars at home and abroad in recent years in the pathogenesis, diagnosis and treatment management of syncope in children and adolescents, all of which provide better diagnosis and treatment ideas for the clinical treatment of syncope in children and adolescents.

Keywords: Children and Adolescents, Syncope, Diagnosis and Treatment

Introduction

Syncope is a common symptom in children and adolescents, and it is more common in girls in children and adolescents, with the incidence peaking between the ages of 15 and 19, but the cause of syncope in most pediatric patients is still unclear, and there are still some difficulties and challenges in diagnosis and treatment. This article reviews the representative new progress made by researchers in recent years in the classification of syncope, the latest progress in pathogenesis, evaluation and diagnosis, and treatment management.

Classification of Syncope

Syncope is classified as autonomic, cardiac, and non-cardiac.

Autonomic Syncope

This is by far the most common cause of syncope in children, once thought to be a single entity, and is now known to include a range of autonomic control abnormalities.

Neurocardiogenic Syncope (NCS), also known as "common faint," is commonly triggered by factors related to neurally mediated syncope, such as orthostatic stress (e.g., prolonged standing or taking a hot bath) or emotional stress (e.g., seeing blood). NCS has been proposed to be caused by a paradoxical reflex known as the Bezold-Jarisch reflex, which is activated when venous pooling reduces ventricular preload [2]. This reduction leads to decreased cardiac output and blood pressure, which are sensed by arterial baroreceptors. The resulting increase in catecholamine levels, combined with reduced venous filling, causes vigorous ventricular contractions and volume depletion.

Orthostatic fainting due to autonomic dysfunction occurs when standing upright causes up to 500 ml of blood to pool in the abdomen and lower extremities, resulting in a sudden decrease in venous return to the heart [3]. This reduction leads to decreased cardiac output, stimulating aortic, carotid, and cardiopulmonary baroreceptors, which trigger a reflexive increase in sympathetic blood flow. As a result, heart rate, cardiac contractility, and vascular resistance increase to maintain stable systemic blood pressure during standing. Although these conditions are common in adults, they are increasingly observed in adolescents [4-5]. Symptoms often appear around the time of rapid growth spurts. Symptoms of orthostatic intolerance include fainting, dizziness, presyncope, tremors, weakness, fatigue, palpitations, sweating, and blurred or narrowed vision. Many adolescents may also experience acrocyanosis due to excessive venous pooling. Orthostatic hypotension is defined as a drop in systolic blood pressure of 20 mm Hg or more, or a drop in diastolic blood pressure of 10 mm Hg or more within three minutes of standing. Autonomic dysfunction-related syncope also occurs in patients with Joint Hypermobility Syndrome (JHS), including syncope, presyncope, palpitations, chest discomfort, fatigue, heat intolerance, orthostatic

hypotension, Postural Orthostatic Tachycardia Syndrome (POTS), and unclassified symptoms of orthostatic intolerance.

Orthostatic hypotension can also be caused by neurogenic causes and can be subdivided into primary and secondary autonomic failure. Primary causes are usually idiopathic, while secondary causes are associated with known biochemical or structural abnormalities or are considered part of a specific disease or syndrome Another inherited autonomic disorder that usually affects children of Ashkenazi Jewish descent is Familial Autonomic Disorder (FD). FD is currently considered to be hereditary sensorimotor neuropathy type III. Clinical features reflect extensive involvement of sensory and autonomic neurons. People with FD experience dysplasia, difficulty sucking and swallowing, impaired thermoregulation, breath-holding, sleep disturbances, and seizures in infancy. Autonomic abnormal syncope caused by orthostatic hypotension is common in adolescents. About 60% of FD patients suffer from breath-holding in the first 5 years of life. Some patients experience autonomic crises such as high blood pressure, tachycardia, excessive sweating, or erythema on the skin.

Orthostatic Tachycardia Syndrome (POTS), currently defined as orthostatic intolerance symptoms associated with an increase in heart rate of 30 or more beats per minute (or more than 120 beats per minute) within 10 minutes prior to standing or upright, without other chronic debilitating diseases. Such as prolonged bed rest or the use of drugs known to affect vascular or autonomic function [6-7].

POTS is now known to cause multiple variants due to these multiple causes, including partial autonomic abnormalities, centrally mediated hyperadrenergic stimulation and norepinephrine transporter dysfunction [8], autoimmune antibodies to anticholinesterase receptors [9], POTS associated with deregulation [10], and hypervolemia A recently published study reported that POTS may be a manifestation of autonomic cardiac neuropathy reported to be associated with trauma [11] , Lyme disease [12], electrocution [12] , multiple sclerosis [13], mitochondrial cell lesions [14], and also related to Atrio Ventricular (AV) node reentrant tachycardia after slow channel ablation.

Breath-Holding Breath-Holding Disorder is usually seen in children and can be roughly divided into two categories. Cyanosis usually appears around 6 months, peaks around 2 years of age, and disappears completely by age 5 years of age with loud crying at the beginning of the attack, followed by apnea. The child's face becomes pale or purple. May be accompanied by convulsive or myoclonic movements or convulsions, followed by lameness. The entire episode lasts less than 1 minute and ends with the child gasping and suddenly taking in a deep breath, color and consciousness returning to normal However, in some severe episodes, recovery is often delayed because the child may remain sleepy for several minutes.

Another form is called a pale breath-holding attack or a reflex hypoxia attack. It usually occurs in children between the ages of 12 and 24 months. This is similar to the form of cyanosis and is usually caused by injury or pain, such as a head impact or sudden startle. The child suddenly stops breathing, contrary to the cyanotic form, does not cry, and the child quickly loses consciousness. The child is pale, blood pressure is too low, and rhythmic muscle contractions appear. These episodes are associated with severe bradycardia and/or cardiac arrest as shown by the monitor. The frequency of these attacks varies greatly, ranging from 2-4 times a day to 1 per year. Almost 30% of children have a similar history of seizures in their family members. There is no specific treatment for these breath-holding episodes. A correct diagnosis and reassurance of parents are needed.

About 50% of children have complete resolution of symptoms by age 4, and 100% of patients have no episodes after age 8. However, it has been reported that up to 25% of people with breath-holding disorder in childhood may develop NCS and attention problems later in their lives. 1.5 Phobia of blood injury Most phobias usually result in a state of hyperadrenergic, and patients with BIP usually have tachycardia. However, a group of children with Blood Damage Phobia (BIP) had paradoxical bradycardia or severe cardiac arrest in response to initial transient tachycardia [15], which often resulted in presyncope or syncope. These children, after a period of time, learn to avoid situations like other children with phobias, because they consider these scenes of injury or bleeding unpleasant. However, unlike other phobias, children with BIP did not have an increased association with other mental illnesses, such as depression.

Some of these children later develop NCS, and there is some clinical evidence of overlap between BIP and breath-holding episodes.

Cardiogenic Syncope

accounts for about 10% of syncope in children and young adults. Cardiovascular disease can be caused by blockage of blood flow, myocardial dysfunction, or arrhythmias.

Primary Myocardial Dysfunction

Cardiomyopathy is rare in children, and syncope in these patients may be due to ischemia, arrhythmias, or neuromuscular dystrophy due to certain inflammatory processes, which can manifest as myocardial dysfunction and chronic arrhythmias caused by atrioventricular block. Myocarditis caused by ventricular tachycardia may also manifest as syncope in children, and unrecognized myocarditis may be an important cause of sudden death in children. Other causes of syncope include Eisenmenger syndrome, tetralogy of Fallot, pulmonary artery stenosis, and right ventricular outflow tract obstruction.

Arrhythmia is One of the Causes of Syncope

In the absence of structural heart disease, arrhythmias are rarely considered the cause of syncope in children [16]. However, patients with long QT syndrome, Brugada syndrome, or short QT syndrome have an inherently structurally normal heart but may be at risk of syncope and sudden cardiac death. Long QT syndrome Patients with long QT syndrome usually present with syncope

related to mood or exercise and have a structurally normal heart. They are prone to pleomorphic ventricular point torsadecardia, which can lead to hemodynamic impairment and subsequent syncope. They may also experience sudden fainting when they are startled or awakened by loud noises, such as alarm clocks.

Arrhythmias can also be caused by structural heart disease that has been repaired or remitted. Sinus node dysfunction has been reported to occur after atrial repair surgery [17-19]. If severe, these patients may develop symptomatic bradycardia and syncope. Similarly, AV block in pediatric patients is either congenital (seen in maternal lupus), which may not require pacing, or acquired infections such as diphtheria, endocarditis, Lyme disease, and Rocky Mountain spotted fever. Ventricular tachycardia, although rare, has been reported in patients with corrected tetralogy of Fallot. Often, these arrhythmias originate near the ventricular tract, especially the ventricular septum and outflow tract. Supraventricular tachycardia, like adults, rarely presents as syncope in children. The most common causes of supraventricular tachycardia, including AV reciprocating tachycardia and AV reentrant tachycardia, have clinical manifestations similar to those in adults.

Non-Cardiac Causes of Syncope

In some individuals, global cerebral hypoxia causes not only loss of consciousness but also convulsive activity. These convulsive syncope seizures are sometimes difficult to distinguish from seizures caused by epilepsy [20]. Autonomous-mediated reflex syncope (such as cardiogenic or vasovagal syncope) can produce sudden deep hypotension and bradycardia, resulting in loss of consciousness and sometimes convulsive activity.

It has been reported that up to a third of patients with initial diagnosis of epilepsy have convulsive seizures actually caused by cardiovascular causes. However, in contrast to convulsive syncope, seizures in epileptic disorders are longer-lasting (1 min), rhythmic, and are usually not caused by stimuli that normally cause syncope. Similarly, many times seizures, especially in neonatal seizures and complex partial seizures with minimal convulsive activity, can be confused with true syncope. It can be difficult to distinguish between the two conditions, especially when there is minimal or no convulsive activity (kinesic seizures). An Electro Encephalo Gram (EEG) may be the only way to distinguish between these seizures and syncope. In the case of syncope, the EEG may be normal or show diffuse slowing of background activity. However, in the case of seizures, background activity is abnormally increased [21]. Another category of disorders that can be very similar to syncope and seizures includes loss of consciousness, which causes complex migraines or basal migraines, sometimes called brainstem attacks, loss of consciousness can also occur in patients with hydrocephalus, who have a sudden increase in intracranial pressure. If hydrocephalus is suspected, neuroimaging may show structural abnormalities such as tumors or brainstem herniations with ventricular dilatation.

The Latest Progress in Pathogenesis

The reasons for these hemodynamic differences between syncope patients and the general population are currently unknown, although the hypotheses that have been put forward question the trend of low circulating blood volume, increased venous cistude volume [22], and abnormal neuroendocrine activation [23]. Recent studies have shown that the neuroendocrine cascade is immediately activated before orthostatic syncope, characterized by adrenaline and antidiuretic hormone release [24-27]. Elevated epinephrine and vasopressin levels during Tilt Testing (TT) are associated with a shorter time to syncope, suggesting that the neuroendocrine system plays an important role in individual syncope susceptibility [24,25].

Individual hemodynamic characteristics not only determine the susceptibility to reflex syncope but also affect TT response. Another recent study showed that patients with tilt-positive had lower systolic BP, diastolic BP, and HR compared to tilt-negative patients with similar manifestations, regardless of age and sex. The above pathophysiological results show a decrease in compensatory capacity for lower systolic blood pressure by reducing diastolic BP and HR. Consistently, decreased resting systolic BP (≤128 mmHg) and absence of hypertension have been identified as independent predictors of TT positivity, confirming that reflex syncope susceptibility is strongly correlated with hemodynamic reserves, which decrease when BP decreases.

Therefore, three different hemodynamic characteristics can be generalized, including: (1) individuals with stable cardiovascular homeostasis; (2) individuals with syncope susceptibility and well-functioning compensatory mechanisms can increase tolerance to orthostatic stress and TT; (3) Due to poor compensatory ability, individuals are more likely to develop reflex syncope during TT.

While studying the hemodynamic characteristics that determine susceptibility to reflex syncope, some studies have gained a better understanding of the hemodynamic changes that occur during TT-induced syncope. The decline in BP that occurs during reflex syncope has traditionally been attributed to vascular inhibition, including a decrease in sympathetic arterial tone and vascular peripheral resistance, as well as cardiac inhibition, including the effects of the vagus nerve on the sinus and atrioventricular nodes, which can lead to pulseless thrombosis.

A recent study by VanDijk et al. suggests a different scenario suggesting that reduced stroke volume is the first determinant of BP decline, with vascular resistance providing only a small contribution. The decrease in stroke volume may be attributed to venous stasis, which is not fully compensated for by increased HR. Cardiac inhibition then begins with a diminished initial compensatory HR increase, which increases BP decline and thus serves as a turning point in the reflex syncope hemodynamic cascade. A detailed analysis of TT responses at different ages showed that the relative effects of cardiosuppression and vascular inhibition varied with age. The prevalence of vascular suppression gradually increases with age, while the cardiosuppressive response shows the opposite trend.

Assessment and Diagnosis

With a detailed medical history and a comprehensive physical examination, almost half of patients successfully determine the

cause of syncope. Unlike adults, obtaining a medical history from a child can be difficult, often from a parent or witness. When obtaining information from a patient or witness, efforts should be made to obtain a detailed description of the situation and activity prior to the event, identified triggers or triggers, the situation during syncope, whether the syncope occurred while standing or lying down, and any symptoms or warning signs prior to the event. Information such as convulsive movements, loss of bladder and bowel control, tongue biting, and rapid or delayed recovery may provide important clues to diagnosis. It is also important to identify patients who may be at risk of sudden cardiac death when taking a medical history.

Laboratory Research

Blood Test: Routine use of blood tests, such as serum electrolytes, heart enzymes, glucose, and hematocrit levels, is not recommended for routine use in patients with syncope because of their low diagnostic value.

Electrocardiogram Examination: Every patient with loss of consciousness, especially after exercise, should have a 12-lead ECG. Particular attention should be paid to the QT interval, preexcitation, bundle branch block, and ventricular hypertrophy for signs of atrioventricular block. ECG evaluation is particularly important if long QT syndrome is possible. If the event appears to be related to exercise or stress and the standard ECG is normal, an exercise ECG should be performed.

Video-Assisted Recording: Video recordings allow doctors to see real episodes and, when combined with physical monitoring, including continuous ECG and EEG, may help improve diagnostic efficiency.

Dynamic ECG Monitoring: Ambulatory ECG monitoring allows patients with greater symptom rhythm correlation to suffer from frequent syncope. If the patient has frequent syncope, external digital monitoring may help reveal potential rhythm disturbances during syncope. If seizures are infrequent, the implantable loop monitor can extend the monitoring time up to 3 years.

Head-Up Tilt Table Test: The Head-Up Tilt Table Test (HUTT) is usually performed for 30 to 45 minutes after a 20-minute horizontal pre-tilt stabilization phase, and the angle is usually performed for 30 to 45 minutes after a 20-minute horizontal pre-tilt stabilization phase with an angle between 60 and 80 (most commonly 70). The sensitivity of the test can be increased by using longer tilt durations, steeper tilt angles, and stimulants such as isoproterenol or nitroglycerin, but the specificity decreases [28-30]. HUTT is safe in children over 6 years of age. It can also be done in younger children if combined. Contrary to studies in adult patients, studies on the use of HUTT in children have been poorly reported.

Echocardiography

Echocardiography is commonly used to evaluate patients with syncope with abnormal ECG or abnormal cardiovascular examination. Echocardiography should be done in patients with suspected structural heart disease.

Imaging Examination

Neuroimaging is not routinely performed in the evaluation of children and young adults with syncope, unless the patient has abnormalities on neurologic examination and may have signs of increased intracranial pressure or focal neurological deficits. Cardiac imaging, including cardiac MRI, rarely needs to evaluate people with suspected coronary artery abnormalities.

Treatment

The treatment of patients with syncope largely depends on the cause and mechanism of syncope. Management of the most common causes of syncope in children (NCS): Management of neurocardiogenic syncope in children: education and comfort, physical countermeasures, rhythmic breathing, fluid therapy, medication, pacemaker therapy, cardiac nerve ablation.

Education and Comfort

Treatment of syncope due to VVS should begin with a careful medical history, with special attention to identifying predisposing factors, quantifying salt intake and current medication use, and determining whether the patient has any pre-existing conditions that may alter treatment. For most patients with neuromediated syncope, especially those with infrequent episodes associated with identifiable triggers, education and reassurance are sufficient.

Physical Confrontation Strategies

Physical training early in the onset of NCS symptoms may help stop the attack. The simplest of these movements is to take a supine position. Subsequently, elevating the legs may lead to increased venous return to the heart. Sitting and squatting may also increase peripheral vascular resistance and improve venous return to the heart. Increased cardiac venous return subsequently increases cardiac output, blood pressure, and cerebral perfusion, and aborts syncope. Crossing the legs in combination with the tension of the thigh and abdominal musculature has been shown to be very effective in preventing reflex syncope in young patients. [31,32] If the patient cooperates, gradually lengthening the duration of forced upright posture or incline training can reduce the recurrence of NCS by reducing the vascular compliance of the chamber primarily responsible for the venous pool. Elevating the head of the bed (BBB10) during sleep can also help improve symptoms. Compression socks can sometimes help, but to be effective, they must be waist-high and provide at least 30 mm Hg of ankle counterpressure. The European Society of Cardiology guidelines for the management of syncope diagnose and treat identifies the following physical measures as level 2 treatments for neuromediated syncope: (1) incline training (2) flat head tilt sleep (BBB10), (3) isometric leg and arm counterpressure movements, (4) moderate aerobic and isometric exercise [33] It has been reported that 2 minutes of isometric grip exercise initiated at the onset of symptoms during the incline test can leave two-thirds of patients asymptomatic. Other studies have shown that inclined (standing) training is effective in treating nerve-mediated syncope. Standing training involves standing against a wall with your heels 10 inches off the wall for a gradual increase in duration for 2 to

3 months. Standing time is initially 5 minutes 2 times a day and gradually increases to 40 minutes 2 times a day. While the results of non-randomized studies of standing training are positive, the results of randomized trials suggest that standing training may have limited effects.

Rhythmic Breathing

In some cooperative patients, breathing training with rhythmic breathing has been shown to prevent inclination-induced NCS. Rhythmic breathing is a deeper, slower way of breathing. It consists of filling your lungs as you inhale and then expelling as much air as you can as you exhale. One study showed that rhythmic breathing can inhibit Hutt-induced syncope.

Fluid Therapy

Increasing the intake of oral fluids and salt is an effective measure to prevent VVS episodes. Patients were also told to drink about 2 L of fluid per day and consume 2 g to 4 g of salt or increase fluid intake until the urine was clear and colorless. In one study, acute oral treatment with 200 mL to 250 mL of water was found to prevent HUTT-induced syncope in 78% of patients who showed HUTT positivity prior to fluid therapy.

Drug treatment

In patients with recurrent syncope, pharmacology may be considered despite education and lifestyle changes, including PCM training. Many medications have been used to treat reflex syncope, but most of the results are disappointing. While the results of uncontrolled or short-term controlled trials are satisfactory, several long-term placebo-controlled prospective trials have not shown the effect of active drugs over placebo, with some exceptions. Currently, the FDA has not approved a treatment for patients with NCS, and there is a lack of evidence to support any drug treatment. The value of pharmaceutical formulations is less certain compared to physical manipulation. Drugs commonly used to treat VVS include b-blockers, flucortisone, serotonin reuptake inhibitors, and midokaine:

β blockers have a negative inotropic effect in reflex syncope and are therefore thought to reduce the activation of ventricular mechanoreceptors. This theory has not been supported by clinical trial results. In two randomised double-blind controlled trials, receptor blockers were ineffective for VVS. There is a lack of rationale for the use of β blockers in other forms of neutral-mediated syncope. It should be emphasized that β-blockers may aggravate bradycardia in patients with CSS.

Flucortisone counteracts the physiological cascade leading to orthostatic vasovagal reflex by increasing renal sodium reabsorption and expanding plasma volume, and its mechanism of action can be compared to saline infusion, which has also been shown to be effective in Preventing Syncope in the Acute Tilt Trial (POST) enrolled 210 young (median age 30 years) patients with low normal arterial BP and no comorbidities, and randomized them to receive fluorocortisone (The titrated dose is 0.05-0.2mg once daily) or placebo. The primary endpoint showed that the incidence of syncope was marginally not significantly reduced in the fluorocortisone group compared to placebo (hazard ratio 0.69, 95% CI 0.46 to 1.03; P=0.069), which became even more significant when the analysis was limited to patients who achieved a stable dose of 0.2 mg/day at 2 weeks. There was little clinical benefit from fluorocortisone treatment: at 12 months, 44% of patients in the fluorocortisone group continued to suffer from syncope, a rate only slightly lower than the rate of 60.5% observed in the placebo group. At the same time, the same number of patients discontinued fluorocortisone treatment due to side effects, resulting in an equal benefit/risk ratio. Fluorocortisone should not be used in people with high blood pressure or heart failure. In a randomized, double-blind small trial in children, fluorocortisone was ineffective. Although these drugs are widely used, none of them have been proven effective in several large prospective randomized clinical trials. Although many researchers previously considered B blockers to be effective treatments, recent studies have reported that the B blockers metoprolol, Xindian, and nadolol are not more effective than placebo.

Pacemaker Therapy

It seems logical that in some patients with Hutt-induced deep bradycardia and sometimes achalpadia arrest, placement of a permanent pacemaker may be beneficial in preventing syncope in this subgroup. However, an important question remains whether these tilt-induced cardiac arrest events accurately reflect what happens at the time of spontaneous onset. Although there are doubts about the use of pacemakers in patients with severe NCS with or without pulsatility, a Spanish study [34] confirmed that pacing significantly reduced syncope events and time to first recurrence in patients with cardiodepressive TT-induced syncope (recurrence rates of 9% and 46%, respectively with biventricular pacing compared with closed-loop stimulation). This conclusion is reinforced by the results of the multicentre randomised placebo-controlled BIOSync trial. It was shown that patients with positive cardiosuppression received biventricular pacing and had a significantly lower risk of syncope recurrence (pre-) syncope (77% lower relative risk and 46% lower absolute risk at 2 years) compared with closed-loop stimulation [35].

Based on this evidence, the European Society of Cardiology (ESC) guidelines elevate the pacing indication for reflex syncope from IIb to I [36]. It must be understood that cardiac pacing is not always necessary and is only for patients aged 0-40 years of age who suffer from severe, recurrent, unpredictable syncope (i.e., usually without prodromal symptoms) with high-risk injury [36]. Currently, there is no evidence to support < need pacing even with severe symptoms in patients aged 40 years [36].

The beneficial effects of pacing are related to the role of HR in the syncopal hemodynamic cascade. If the sensor is ideal, pacing can prevent a decrease in HR at the onset of cardiac depression. The increase in HR will combat bradycardia and cardiac arrest and limit BP decline. This largely depends on the fine-tuning of the sensor to the individual's needs. Patients with a susceptibility to hypotension may be at risk of syncope recurrence after pacing due to persistent vascular inhibition. Due to the coexistence of

bradycardia and hypotension phenotypes, syncope recurs after pacing in approximately 15% to 20% of patients [37,38,39,40]. In addition to pacing, specific therapeutic interventions for hypotensive susceptibility are necessary to minimize the risk of relapse.

Cardiovascular Ablation

Cardio Neuro Ablation (CNA) is an endocardial electrophysiological procedure in which parasympathetic nerve fibers are extraferently removed from the epicardial ganglion to induce partial parasympathetic sinus and atrioventricular node denervation [41-43]. CNAs reduce vagus nerve drive to the heart, mediating reflex cardiac depression. It was proposed by JCPachon in 2005 [43]. Preliminary data from case series and observational studies suggest that vagus denervation is successful and beneficial for syncope burden [43-46]. However, the available evidence on CNA is very limited, and the methods and long-term consequences of denervation remain uncertain [47,48]. There are currently no randomised controlled trials. There have been reports of the use of radiofrequency energy (similar to ablation of atrial fibrillation) in patients with refractory NCS to target the ganglion plexus of the left and right atrium, thereby eliminating the Bezold-Jarisch reflex. The procedure, known as cardiac nerve ablation, is encouraging and significantly reduces the recurrence rate in patients with refractory syncope [49-52]. However, these results need to be confirmed in large randomized controlled trials. Therefore, the use of CNAs is currently experimental and more evidence is needed.

Future Prospects

There is little literature in the field of syncope in children and adolescents. Management strategies for most children reflect data from studies involving adult populations. There will be a great need for research in children and adolescents with recurrent syncope in the future. In addition, there is no FDA-approved treatment for NCS so far, which is the most common cause of syncope in adults and children. In NCS, none of the clinical trials of drug therapy showed superiority over placebo. One potential reason is that most of these trials are flawed or have unreasonable endpoints. Most of these clinical trials look at the “time to first syncope”, which may not be a reasonable endpoint for assessing the success of any treatment. NCS should be considered a chronic disease, and like other chronic diseases, treatment should be aimed at reducing the recurrence of syncope rather than eliminating it completely. When designing new clinical trials, more reasonable endpoints, such as syncope burden, are needed. In the future, it is hoped that there will be data on the medical treatment of NCS and its variants, including POTS and other forms of abnormal autonomic syncope.

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Conflict of Interest

None.

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