Autonomic Syncope in Pediatrics: A Practice-Oriented Approach to Classification, Pathophysiology, Diagnosis, and Management

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Summary: This paper presents a practice-oriented approach to the problem of syncope in pediatrics. Autonomic syncope is the major etiologic category in pediatrics and consists of 2 types: reflex and dysautonomic. The latter type is rare in pediatrics. Reflex syncope has 4 subtypes: neurocardiogenic, central, situational, and cerebral. Neurocardiogenic syncope, the most common subtype, is easily diagnosed by taking a careful, detailed history; identifying diagnostic red flags; performing a complete physical examination; and ordering a minimum of laboratory tests. Patient and parent education is essential, and usually, without medication, outcomes are good. *Clin Pediatr.* 2004;43:17-23

Introduction

Doctor visits for syncope increased significantly in the 1990s compared to previous decades.[1] A likely reason was increased media and legal interest in the sudden deaths of athletes, which frightened parents, coaches, and teammates and also increased physician concern. Syncope in children and adolescents is common, with 15% estimated to have had at least one syncopal episode by age 18, and it is usually benign and easily managed.[2] However, many classifications, long lists of possible etiology, and therapy, mostly based on adult experience, have been published in pediatric texts and journals. The author's objective, based on many years of personal experience and review of the literature, is to offer a pediatric-oriented, less formidable, more concise, practical approach to syncope for the primary care physician.

Syncope is generally defined as a sudden, brief loss of consciousness and postural tone, usually preceded by a very short period of premonitory symptoms and signs called presyncope, and followed by a spontaneous, rapid, and complete recovery. Syncope is thus a very specific type of loss of consciousness, and usually different from the loss of consciousness that may occur with many other conditions such as seizures, hypoglycemia, drug overdose, and head trauma.

The etiology of most cases of syncope can be placed into 1 of 5 categories: (1) autonomic, (2) cardiac, (3) psychiatric, (4) neurologic/cerebrovascular, and (5) metabolic/endocrine (Table 1). Autonomic syncope is by far the

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most common etiology in pediatrics, followed by cardiac and psychiatric syncope. Categories 4 and 5 are rare.

Autonomic Syncope

A minimal mean arterial blood pressure, the major determinant of cerebral perfusion, is essential for maintaining consciousness. The human autonomic nervous system regulates the blood pressure through a very efficient reflex system. It uses pressure sensors in the walls of the pulmonary artery, the arch of the aorta, and the internal carotid arteries (baroreceptors) and also, perhaps, in the ventricular myocardium (mechanoreceptors). Changes in posture, cardiac output, or blood volume send signals from these pressure sensors to the medulla via afferent vagal C-fibers. Appropriate changes in heart rate, ventricular and blood vessel contractility, and blood volume are then made by neurohormonal transmitters to maintain adequate cerebral perfusion and consciousness.

In defining autonomic syncope, note, first, that syncope is a symptom, like headache, and not necessarily associated with a disease. Second, autonomic syncope is a sudden, clinical event, caused by a temporary dysregulation of the autonomic nervous system. Third, autonomic syncope may be an isolated variant of normal autonomic function, or it may be part of a disease process involving the autonomic nervous system.

There are 2 major types of autonomic syncope: (A) reflex syncope, a hyperresponsive type and the main focus of this presentation, and (B) dysautonomic syncope, a hyporesponsive type, rarely seen in pediatrics (Table 2).

Table 1

ETIOLOGIES OF SYNCOPE*

1. Autonomic Syncope
2. Cardiac Syncope
3. Psychiatric Syncope
4. Neurologic/Cerebrovascular Syncope†
5. Metabolic/Endocrine Syncope†

*As defined in text; †Rare in pediatrics.

Table 2

AUTONOMIC SYNCOPE— TYPES AND SUBTYPES IN PEDIATRICS

A. Reflex Type (hyperresponsive)

Subtypes:

1. Neurocardiogenic syncope
2. Central syncope
3. Situational syncope
4. Cerebral syncope

B. Dysautonomic Type (hyporesponsive)*

Examples of diseases:

—Familial dysautonomia (Riley-Day syndrome)

—Dopamine beta hydroxylase deficiency (DBH)

—Norepinephrine tramsporter deficiency (NET)

—Postural orthostatic tachycardia syndrome (POTS)

*Rare in pediatrics.

A. Reflex Syncope

This is an exaggerated normal response to a stimulus or trigger. It accounts for almost all of the autonomic syncope cases encountered in pediatrics and there are 4 subtypes: neurocardiogenic, central, situational, and cerebral syncope.

Neurocardiogenic Syncope. This is the most common subtype of reflex syncope and is reported in the literature to be the etiology in 50% to 80% of pediatric patients presenting with syncope. Historically known as the common faint, it was named vasovagal syncope by Sir Thomas Lewis, a famed British

cardiologist, in 1932, and subsequently also called vasodepressor syncope and neurally mediated syncope. The name *neurocardiogenic syncope* was first introduced in 1990 to better describe the presumed pathogenesis of this clinical entity.

The trigger is peripheral, namely, orthostasis, and the response is peripheral, with significant bradycardia or hypotension, or more frequently, both.

The presumed pathophysiologic mechanism of neurocardiogenic syncope, until recently, has been activation of the "Bezold-Jarisch" (B-J) reflex. First proposed by Albert von Bezold in Germany in 1867 and later supported by the work of Jarisch in 1937–1948, it was demonstrated in animals and thought to be an inhibitory reflex designed to protect the left ventricle from excessive pressure. Thus, if the pressure rises suddenly, ventricular mechanoreceptors will be activated and send signals to the medulla via vagal fibers, causing parasympathetic stimulation and sympathetic withdrawal. The result is bradycardia and/or hypotension, decreasing the load on the ventricle. It is further postulated that in some individuals, with sudden or prolonged standing, enough blood pools in the lower part of the body to decrease venous return and produce a relatively "empty heart." To maintain cardiac output, there are vigorous ventricular contractions, activating these ventricular mechanoreceptors. This leads to the B-J reflex response with marked bradycardia and/or hypotension and syncope.

The activation of this reflex, whose purpose, presumably, is to protect the heart from high pressure, instead leads to an inappropriate and paradoxic loss of consciousness. Many reasons for this paradoxic response have been proposed, and include beta-adrenergic hypersensitivity, impaired peripheral vasoconstriction, and abnormal serotonin neurotransmission.[3,4] Recently, however, several investigators have questioned the role of any ventricular mechanoreceptors in initiating the paradoxic parasympathetic response leading to syncope. Other mechanisms have been proposed, including a primary baroreceptor or central nervous system role, but the consensus is that the exact pathophysiology of neurocardiogenic syncope is still a mystery.[5-10]

Neurocardiogenic syncope is more frequent in adolescents and in females. Many patients with syncope have a parent or sibling who has also fainted. The usual triggers are an abrupt change in position from supine or sitting to standing, or prolonged standing. Syncope may also occur during walking or immediately after exercise. Contributing factors include dehydration, heat, crowding, stress, illness, anemia, and high basal vagal tone. Neurocardiogenic syncope can be divided into 3 clinical stages.

1. Presyncope.
   The onset is abrupt. Symptoms include weakness, light-headedness, dizziness, visual changes (described as vision becoming blurred, dim, dark, tunnel-like, or seeing black spots), headache, tinnitus, salivation, palpitations, epigastric discomfort, nausea, vomiting, and a feeling of "about to pass out." Signs include pallor, yawning, sighing, sweating, hyperventilation, bradycardia, and/or hypotension. The duration is brief, usually only 10 to 20 seconds.

2. Syncope.
   The individual is unconscious, flaccid, and pale or ashen; the pupils are dilated; the body is covered with sweat; the skin is cold; and the pulse is weak and slow. There may be urinary incontinence and tonic/clonic limb movements, which some have called "convulsive syncope." The duration is seconds to a few minutes

3. Post-syncope
   The individual feels weak, dizzy or light-headed, nauseated, and often has a mild headache. Full recovery is rapid, usually within one-half hour.

DIAGNOSIS OF NEUROCARDIOGENIC SYNCOPE. The diagnostic evaluation of a patient referred for syncope must include, first, a detailed history. This cannot be overemphasized. Speaking to a witness of the syncopal event is extremely important. The diagnosis of neurocardiogenic syncope should be a positive one and not one made by exclusion. If the history fits the typical clinical picture, the diagnosis can be made with confidence.

A thorough physical examination is also essential. Anemia should be ruled out in menstruating females. An electrocardiogram should always be obtained because, occasionally, there is an unexpected finding that might point to the cause of the syncope, such as the Wolff-Parkinson-White pattern, a long Q-T interval, a conduction abnormality, or evidence of ventricular hypertrophy. Routine echocardiography has a low yield and is not recommended.[11] A tilt test is also not done routinely, for reasons to be discussed later. If the diagnosis of neurocardiogenic syncope cannot be made with certainty, then

without further testing by the generalist, it is usually best to refer the patient to either a neurologist or pediatric cardiologist, depending on the patient's history and physical examination.

Diagnostic red flags must be carefully considered before a final diagnosis of neurocardiogenic syncope is made. Bodily injury is uncommon with neurocardiogenic syncope but does occur, depending on where and how the individual happens to fall.

A cardiac basis must be excluded. Clues include a history of a cardiac problem in the patient or the family, or sudden unexplained deaths in young family members. Palpitations or an absent or very short prodrome, lasting less than 5 seconds, raise the possibility of an arrhythmia. Supraventricular tachycardia only occasionally causes syncope. Ventricular arrhythmias are more likely to cause syncope and may be due to the long QT syndrome or the Wolff-Parkinson-White syndrome or be secondary to preexisting congenital or acquired heart disease. Sinus or atrioventricular (AV) node dysfunction may produce significant bradycardia and syncope. Syncope during exercise is a red flag for a cardiac etiology and will be discussed further.

A seizure disorder should be considered if there is any of the following: a flushed facies, frothing at the mouth, tongue biting, head turning, defecation, loss of consciousness for more than 5 minutes, an atypical recovery period that is prolonged or associated with disorientation, a severe headache, or no memory of a spell.

Clinical use of the head-up tilt test for the diagnosis of syncope in adults was first reported in 1986 and quickly became popular. However, routine pediatric tilt testing, in my experience and that of others, has a low diagnostic yield with too many false-positive and false-negative results, and should not be used as the gold standard for the diagnosis of neurocardiogenic syncope.[12,13] Tilt testing also is not a good predictor of recurrences or of the effectiveness of prophylactic treatment.[14] It may help, however, if there is an inadequate or confusing history, and the tilt produces symptoms that are identical to those the patient has tried unsuccessfully to describe.

TREATMENT OF NEUROCARDIOGENIC SYNCOPE. The first step in treating neurocardiogenic syncope when the diagnosis is made is to reassure the patient and parents that this is a benign condition and that, in most cases, it will respond to simple measures. Next is an explanation of the syncope mechanism, done effectively by describing the B-J reflex. This helps the patient to understand the rationale for the preventive measures to be outlined.

Prevention of dehydration is stressed, and the patient is advised to drink enough fluids to urinate several times a day and keep the color of the urine pale. Caffeine, as is found in coffee and cola drinks, is a diuretic and should be avoided. Salt should be added to the diet during hot weather.Venous pooling in the lower part of the body can be minimized by advising patients to start moving their legs before they arise from a lying or sitting position, and to keep moving them when standing in line, the purpose being to make the leg muscles force more blood up to the heart. If prodromal symptoms begin despite these measures, patients are advised to immediately do one or more of the following: lie down if possible, squat, contract the abdominal muscles, cross the legs, or place one leg up on a stool or step.

In my experience, almost all pediatric patients with neurocardiogenic syncope do very well with the above-outlined approach and have few or no recurrences. There are a few published observational pediatric short-term outcome studies, but they are not comparable in regard to diagnosis, patient mix, or treatment. Long-term pediatric follow-up studies are also scarce. In one retrospective study, 44 pediatric patients were followed up for a mean of 13.9 ± 10.4 months, and all reported either a decrease or no recurrence of syncope, with only 3 still taking any medication.[12] In a prospective study of 97 pediatric patients, followed up for a mean of 46 ± 28 months, the recurrence rate was 32%, with the only positive predictor of recurrence being the number of historical syncopal episodes.[14]

If symptoms recur frequently, then medication can be tried. In 1999, Calkins[15] listed 17 drugs, in addition to extra fluids and salt, that have been prescribed for this type of syncope, but only 3 of these agents had been evaluated in prospective, randomized, placebo-controlled studies. Both midodrine, a peripheral vasoconstrictor, and paroxetine, a selective serotonin reuptake inhibitor, decreased recurrences, but not atenolol, a selective beta-1-adrenergic blocker and also hydrophilic (lacking central nervous system activity). Subsequent studies have attempted to evaluate the effectiveness of different beta-blockers, comparing their selective and nonselective receptor-blocking actions and their lipophilic characteristics, i.e., their ability to enter the central nervous system. However, in a very recent editor-

ial, commenting on effective treatment for neurally mediated syncope, Kapoor,[13] a veteran syncope investigator, concluded that the effectiveness of therapy for prevention of recurrences is open to question, that the results of most drug treatment trials have been disappointing, and that no clearly effective drug has emerged.

For pediatric patients, if there are frequent recurrences, 3 drugs, with minimal side effects, reported to be effective in uncontrolled studies, are available These are fludrocortisone, which primarily increases intravascular volume; a beta-adrenergic receptor blocker, which may decrease ventricular contractility; and pseudoephedrine, which produces peripheral vasoconstriction. Permanent cardiac pacing has been reported to be beneficial in some pediatric patients who have failed pharmacologic treatment.[16] However, Kapoor,[13] commenting on the recent and first randomized, controlled, and double-blinded pacemaker trial, concluded there is no evidence thus far of effectiveness for patients with neurally mediated syncope.

Central Syncope. The trigger arises within the central nervous system, and the physiological response is peripheral, with bradycardia and/or hypotension and syncope. The trigger is usually a strong emotional event or situation that leads to a faint. Central syncope can also be psychiatric in origin, and at times difficult to diagnose. Ictal-bradycardia, a rare form of complex partial seizures, has a central, temporal lobe trigger that causes sudden sinus node arrest and/or AV nodal block, producing syncope.

Situational Syncope. There are many different peripheral triggers, excluding orthostasis, and the physiological response is also peripheral, with significant bradycardia and/or hypotension and syncope. At least 28 different triggers have been reported and are listed in Table 3. Of these, syncope during and after exercise is of particular importance.

Postexercise hypotension, first reported in the 1920s, was called "Die Sportkrankheit" (sport sickness) in Germany in 1930. Eichna,[17] in 1949, described the effect of extreme exertion in soldiers who, immediately after stopping their activity, were tilted for 5 minutes. One third developed significant hypotension and one fourth had syncope. Dehydration and peripheral vasodilatation, which may last for an hour or so after the activity is stopped, were the presumed mechanisms. Anecdotally, physician visits for postexercise syncope seem to increase in hot weather. If the clinical picture is typical, and an ECG appears normal and also hematocrit values in females are normal, further work-up is not indicated. However, these patients should be advised to increase their water intake before and during the activity, to have a warm-down period, and to lie down or squat immediately after stopping the exercise.

Syncope during exercise is much less common. It should be treated with greater concern because in various reports of sudden death in athletes, from 17% to 86% were said to have had one or more prior episodes of syncope before the fatal episode. Conse-

Table 3

SITUATIONAL SYNCOPE TRIGGERS*

Airway stimulation	Hot tub
Breath-holding	Micturition
Carotid sinus pressure	Migraine
Cold drinks	Oculovagal
Cough	Postprandial
Defecation	Procedures
Diving	Shaving
Exercise	Sneezing
Glossopharyngeal	Stretching
Hair combing	Swallowing
High altitude	Trumpet blowing
Hot showers	Valsalva
Hyperventilation	Vomiting
Immunization	Weight Lifting

*Reported in the literature.

quently, it is reasonable to refer all patients with syncope during exercise to a pediatric cardiologist for evaluation to rule out a cardiac etiology.

Cerebral Syncope. The trigger is peripheral, namely, orthostasis, and the physiologic response is central. There is no significant bradycardia or hypotension, but decreased cerebral blood flow has been documented, presumably due to cerebral vasoconstriction, leading to syncope. Thus, measurement of cerebral blood flow during a tilt test is required to establish the diagnosis. This entity, recently described in adults, and occasionally seen in adolescents, may be misdiagnosed as psychiatric syncope.[18]

B. Dysautonomic Syncope

This is a diminished and abnormal autonomic response to a stimulus or trigger, and compared to reflex syncope, is rare in pediatrics.These diseases are mostly genetic in origin and demonstrate a wide variety of symptoms and signs due to autonomic failure, including orthostatic intolerance, orthostatic hypotension, and occasional syncope. There are several examples. Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive condition. Dopamine beta hydroxylase deficiency (DBH) leading to an inability to synthesize norepinephrine is also autosomal recessive.[19] The postural orthostatic tachycardia syndrome (POTS) has been described in some adolescents who have disabling postural sinus tachycardia, lightheadedness, fatigue, palpitations, exercise intolerance, and cognitive impairment. The diagnosis of POTS can be made with a tilt test, using established criteria, and treatment with a selective serotonin reuptake inhibitor is effective.[20,21] POTS is one of a host of other conditions with chronic orthosatic intolerance, one of which has a mutation of the norepinephrine transporter gene (NET), causing impaired norepinephrine uptake.[21] A Japanese report suggested that a serotonin transporter gene abnormality was a risk factor for sudden death in infancy.[22]

Conclusion

Caring for the pediatric patient with syncope, compared to the adult with cardiac and many other possible causes of syncope, should not be difficult for the primary care physician. It will be a successful and rewarding experience if one understands the underlying autonomic nervous system physiology, uses the simple etiologic classification presented, and knows the clinical features of the common entities. Further, enough time must be allotted to obtain a detailed history, consider the diagnostic red flags, do a complete physical examination, obtain the essential laboratory data, and importantly, educate the patient and family about syncope and its prevention.

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