Approach to Syncope and Altered Mental Status

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KEYWORDS

• Pediatric • Syncope • Transient altered mental status
• Persistent altered mental status • Seizure

KEY POINTS

- Although altered mental status (AMS), transient or persistent, can cause a great deal of anxiety for patients and providers, a rational approach to these patients is essential to avoid underuse or excessive use of testing.
- An age-based approach is important, because the various diseases are common in different age groups.
- In patients with transient AMS, differentiating true syncope from other causes is the first step; a stepwise approach, guided by the history and physical examination, can then proceed.
- Persistent AMS, on the other hand, is a life-threatening presentation and time is of the essence.
- The differential diagnosis is broad and, rather than trying to recall long lists of highly specific causes, it is more helpful to consider broad categories of disease: structural lesions, insufficient delivery of appropriate substrate to the brain, metabolic imbalance, inflammation, infection, and abnormal electrical activity.
- Maintaining a broad differential and evaluating for multiple diseases simultaneously is critical in the care of these patients.

INTRODUCTION: NATURE OF THE PROBLEM

Altered mental status (AMS), whether transient (t-AMS) or persistent (p-AMS), presents a diagnostic challenge. With a broad differential diagnosis, a wide range of severity, and potential involvement of any organ system, this presentation is complicated by

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an inability of the patient to give an accurate history. For the purposes of this article, the term AMS is used to describe any change in the way a patient interacts with their environment. What is distinguished is the concept of t-AMS and p-AMS, because the differential is different for these presentations.

For teaching purposes, mnemonics have been developed to help clinicians consider all possible causes of AMS. This long list of possible diagnoses is cumbersome and difficult to remember. Instead, it may be simpler to consider broader categories of disease. For the brain to function normally, it requires adequate perfusion with appropriate delivery of oxygen, nutrients, and balanced electrolytes. In addition, there cannot be structural disease; masses, blood, and excessive cerebrospinal fluid (CSF), which can all impede normal function. It cannot be plagued by infection or inflammation, and electrical activity has to be organized. Some causes more commonly cause t-AMS (moments of inadequate perfusion, abnormal electrical activity), whereas others cause persistent symptoms (structural, metabolic, or infectious).

A detailed description of all causes of AMS is beyond the scope of this article; trauma and toxicology are not discussed. Instead, a description of some of the more common causes is delineated. As these potential causes are reviewed, there are some key themes that must be considered. First, the differential diagnosis for AMS changes with age (**Table 1**). Second, t-AMS is common and usually benign, whereas p-AMS is less common, carries a higher morbidity and mortality, and requires rapid diagnosis and treatment. There is no substitute for a thorough history and physical examination with these patients; it is essential for guiding diagnostic workup.

Table 1
Breakdown of common causes of t-AMS and p-AMS by age

Infants/Toddlers	School Age	Adolescents
t-AMS		
Seizure	Seizure	Seizure
Trauma	Trauma	Trauma
Sepsis	Migraine	Psychiatric causes
ALTE	Syncope	Syncope
BHSs	—	—
p-AMS		
Seizure	Seizure	Seizure
Trauma	Trauma	Trauma
Shock	Shock	Shock
Toxicologic	Toxicologic	Toxicologic
Electrolyte abnormality	Electrolyte abnormality	Electrolyte abnormality
Sepsis/encephalitis	Encephalitis	Encephalitis
Inborn errors of metabolism	Hyperglycemia or hypoglycemia	Hyperglycemia or hypoglycemia
Hypoglycemia	Brain mass	Brain mass
BHSs	Postictal state	Postictal state
Intussusception	Shigellosis	Posterior reversible encephalopathy syndrome

CAUSES FOR T-AMS

Apparent Life-Threatening Event

Defined in 1986 by the National Institutes of Health as an episode that is "frightening to the observer" and has some combination of apnea, color change, change in motor tone, and choking or gagging, Apparent life-threatening events (ALTEs) are the most common presentation of t-AMS in young infants. As is evident by the definition itself, it is impossible to distinguish whether these ALTEs were caused by a cerebral perfusion problem or abnormal electrical activity, and they are difficult to assign to a particular disease.[1] In the neonate, it is prudent to consider sepsis as a possible cause; however, recent literature[1] has shown that bacterial infections, cardiac abnormalities, and structural neurologic diseases are rare. Child abuse and neglect should be considered in these patients, because they have a higher incidence than the general population. The workup for these children is controversial; most of the literature points to a varied, expensive, and low-yield evaluation when these cases are looked at retrospectively. A prudent workup for the child in whom neither sepsis nor nonaccidental trauma is a concern, is a hemoglobin test, electrocardiography (ECG), and a brief period of observation.[2]

Breath Holding

Breath-holding spells (BHSs) present in young children from 6 months to 6 years of age; 80% to 90% present by the time the child is 18 months of age. The classic presentation of BHS is a toddler who throws a tantrum, suddenly holds their breath, turns blue, and then passes out. When consciousness is regained, the child seems fine. The term BHS is inaccurate because it implies that it is an act of volition when it is involuntary.[3] There are 2 varieties of BHS: pallid (after minor trauma and related to bradycardia) and cyanotic (failure to inhale after forced expiration); both start with an inciting event such as emotional upset or minor trauma. In both cases, the child can have loss of consciousness, seizurelike activity, including tonic-clonic movements, and urinary incontinence. Children can have both types of spells and can have numerous episodes per day. Diagnosis is made by historical features. Various treatments have been found to be effective, including supplemental iron for those children who have iron deficiency anemia, serotonin reuptake inhibitors, and pacemaker placement for those with frequent and severe spells.[4,5]

Seizure

Seizures are a common phenomenon, with an estimated lifetime prevalence of 5 to 10/1000.[6] In 1 multicenter study of adults and children,[7] seizure was the presenting diagnosis for 1.2% of visits to the emergency department (ED). Distinguishing seizure from syncope and BHSs can be difficult. The patient can be found in a postictal state, or the seizure type itself can be subtle. There are some pediatric partial seizure types, such as Panayiotopoulos syndrome, which cause episodes that seem to be syncopal. Patients with this benign form of epilepsy can present with sudden loss of muscle tone and unresponsiveness as their only symptom.[8] Although it is tempting to order a computed tomography (CT) scan for patients who present with first-time seizure, if the infant is asymptomatic at the time of presentation, this is unlikely to show any disease and exposes children to unnecessary radiation. A more prudent evaluation would be referral to a pediatric neurologist for magnetic resonance imaging (MRI) and electroencephalography (EEG) as an outpatient.

Syncope

Syncope is the most common cause of t-AMS. It is characterized by rapid onset, short duration, and spontaneous complete recovery.[9] The mechanism for syncope is global decrease in cerebral perfusion, resulting from a decrease in systemic blood pressure (BP). This mechanism differentiates syncope from other causes of transient loss of consciousness (T- LOC) (**Fig. 1**). Because BP is determined by cardiac output and total peripheral vascular resistance, any decrease in either the cardiac output (cardiac syncope) or total peripheral vascular resistance (syncope secondary to orthostatic hypotension) can result in cerebral hypoperfusion. However, the most common type of syncope, reflex syncope, is a combination of both these pathophysiologic mechanisms (**Fig. 2**).

Syncope is usually benign. **Box 1** summarizes various causes of syncope based on mechanism. Reflex syncope, the most common form, is rare in children younger than 10 years but then increases in incidence dramatically, with a peak around 15 years of age.[10] As many as 15% to 20% of all children may experience a syncopal episode before the end of their second decade of life, and lifetime cumulative incidence of reflex syncope in young subjects is 18% to 47%. This finding is in contrast to that of epilepsy (0.5%) or cardiac syncope.[11] Cardiac syncope or syncope secondary to cardiovascular disease (whether structural or arrhythmogenic) is less common, making up 2% to 6% of all cases of pediatric syncope (**Box 2**).[10]

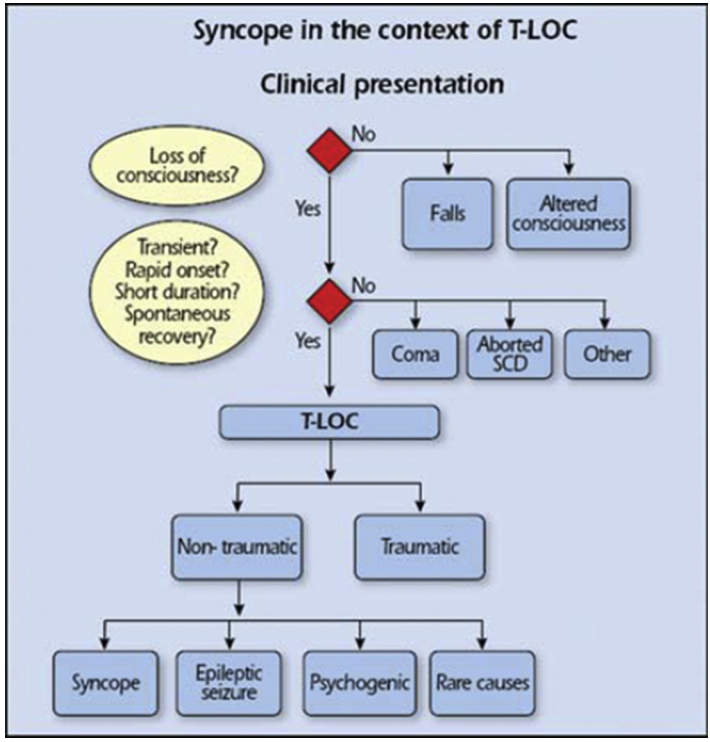

Fig. 1. Syncope in the context of transient AMS. SCD, sudden cardiac death. (*From* Moya A, Sutton R, Ammirati F, et al, The Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC). Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30(21):2635; with permission.)

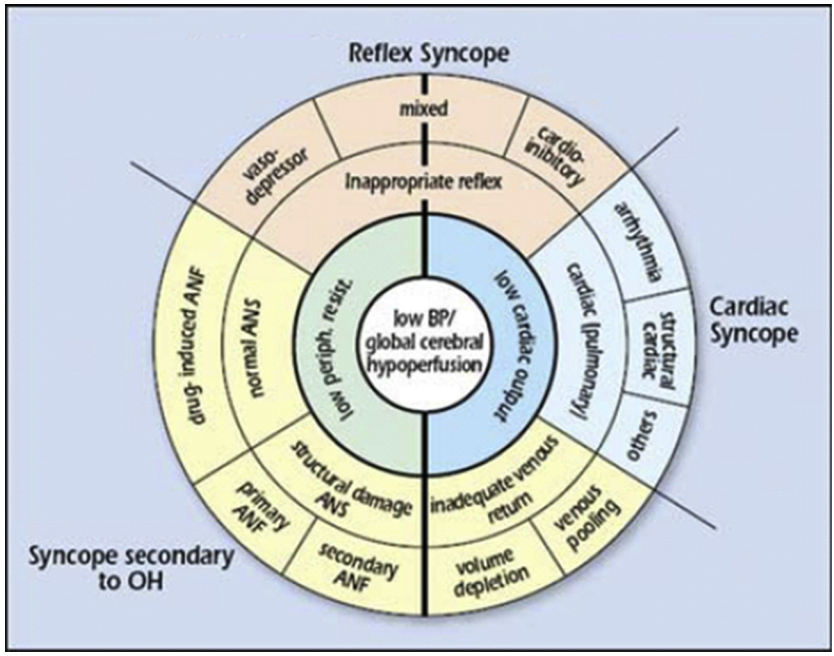

Fig. 2. Pathophysiologic basis of the classification of various types of syncope. ANF, autonomic nervous failure; ANS, autonomic nervous system. (*From* Moya A, Sutton R, Ammirati F, et al, The Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC). Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30(21):2637; with permission.)

Box 1
Pathophysiologic classification of syncope

1. Neurally mediated/reflex syncope (most common cause in children)
   - A. Vasovagal
     - a. Orthostatic stress (common trigger)
     - b. Other triggers (fear, pain, sight of blood)
   - B. Situational (cough, sneeze, defecation, micturition, postprandial, postexercise)
   - C. Atypical forms (without apparent trigger or atypical presentation)
2. Cardiac syncope (risk of SCD) (see **Box 2** for complete list of causes)
   - A. Arrhythmia as the primary cause
   - B. Structural/functional heart disease
3. Syncope caused by orthostatic hypotension (uncommon cause in children)
   - A. Autonomic failure (primary or secondary)
   - B. Drug induced (vasodilators, diuretics, phenothiazines, antidepressants)
   - C. Volume depletion (hemorrhage, diarrhea, vomiting)

Box 2
Causes of cardiovascular syncope: potentially fatal if unrecognized

1. Arrhythmias
   - A. Bradyarrhythmias
     - a. Sinus node dysfunction (especially in patients with congenital heart defects)
     - b. AV block
     - c. Kearnes-Sayre syndrome
     - d. Pacemaker malfunction
   - B. Tachyarrhythmias
     - a. Supraventricular
       1. WPW
       2. Supraventricular tachycardia/atrial arrhythmias (especially in patients with congenital heart defects)
     - b. Ventricular: ventricular tachycardia/torsades/ventricular fibrillation
       1. Channelopathies
          - a. Long QT syndrome
          - b. Catecholaminergic polymorphic ventricular tachycardia
          - c. Brugada syndrome
          - d. Short QT syndrome
       2. Drug induced
       3. Idiopathic
          - a. Ventricular fibrillation
          - b. Outflow tract
2. Structural/functional heart disease
   - A. Cardiomyopathy
     - a. Hypertrophic cardiomyopathy
     - b. Dilated cardiomyopathy
   - B. Coronary anomalies
     - a. Anomalous origin
     - b. Kawasaki disease
   - C. Valvar aortic stenosis
   - D. Arrhythmogenic right ventricular dysplasia
   - E. Acute myocarditis
   - F. Congenital heart disease (repaired and unrepaired)
   - G. Pulmonary hypertension, pulmonary embolus
   - H. Aortic dissection (Marfan syndrome)
   - I. Cardiac masses

Reflex Syncope

Reflex syncope is also known as neurally mediated, neurocardiogenic, or vasovagal syncope. Cardiovascular reflexes that control the circulation become intermittently inappropriate, in response to a trigger, resulting in vasodilatation from a decrease in efferent sympathetic activity or bradycardia or asystole from an increase in the vagal discharge and thereby in a decrease in arterial BP and global cerebral perfusion (see **Fig. 2**).

Cardiac Syncope

Many of the children with cardiovascular disorders who go on to experience sudden cardiac arrest (SCA) have syncope or presyncope as the warning symptom. Identifying this subset amongst all patients who present with syncope is challenging. In a study evaluating warning signs in children and young adults with SCA, 72% had at least 1 cardiovascular symptom before their cardiac arrest (recent fatigue, near-syncope, lightheadedness, chest pain, palpitations, and shortness of breath); nearly a quarter of the SCA victims had at least 1 objective warning event (syncope or unexplained seizure activity), which remained undiagnosed as a cardiac disorder before the cardiac arrest.[12] Previous literature has reported 17% to 25% of young athletes with sudden nontraumatic death have a previous history of syncope.[13,14]

Syncope and Sudden Cardiac Death in Athletes

Because incidence of syncope peaks in adolescence, syncope is not uncommon is athletes. However, exertional syncope is a major red flag and warrants high index of suspicion for underlying cardiac disease. It is critical to differentiate if the syncopal event was unrelated to physical activity (most likely benign reflex syncope), was postexertional (most likely postexertional postural hypotension and again benign) or truly exertional (high chance of an underlying cardiac disease). In 1 study,[15] nearly 6% of all athletes had syncope, of which 13% had exercise-related syncope. However, exertional syncope was only in 1.3% of all athletes who fainted, and 2 of 6 (ie, one-third of the athletes with true exertional syncope) had a cardiac diagnosis. One study summarizing the cause of death in young competitive athletes in the United States over a 27-year period[16] found a cardiovascular cause in 1049 (56%) of all 1866 deaths. Hypertrophic cardiomyopathy (HCM) (36%), coronary anomalies (17%), myocarditis, arrhythmogenic right ventricular cardiomyopathy, and channelopathies were the most common cause identified (see **Box 2**).

HCM

HCM is an autosomal-dominant condition that affects 0.1% to 0.2% of the general population and is the most common cause of sudden cardiac death (SCD) in the young. HCM has a wide clinical spectrum, ranging from asymptomatic patients to patients with heart failure, left ventricular outflow tract obstruction, atrial arrhythmias, or syncope/sudden death as the initial presentation. Nearly 21% of athletes who died of HCM had some signs or symptoms of cardiovascular disease before death.[14] Arrhythmias are responsible for syncope and sudden death in these patients. There may be a history of exertional symptoms or a family history of HCM or sudden death. Physical examination is mostly normal. An ejection systolic murmur pronounced on standing can be heard in the obstructive form. ECG is helpful in the diagnosis and is abnormal in nearly 95% of patients with HCM, with findings of left ventricle hypertrophy, left axis deviation, T wave abnormalities, or abnormal Q waves. However, echocardiography is diagnostic. All patients should avoid competitive sports. Treatments modalities

include β-blockers, calcium channel blockers, heart failure management, myectomy, antiarrhythmics, and implantable cardioverter defibrillator (ICD) placement depending on the clinical status.

Coronary Artery Anomalies

Reported incidence of anomalous origin of coronary artery from opposing sinus is 0.17% and it is the second most common cause of SCD in athletes.[17] As with HCM, SCD can be the initial presenting event. However, nearly half of the patients may have signs of cardiovascular disease before their death.[18] Syncope with exercise is the hallmark clinical feature, because hemodynamic changes during exercise may exacerbate compromised myocardial perfusion. Ventricular arrhythmia (**Fig. 3**) is the cause of syncope or death. Echocardiography can miss these anomalies if not evaluated carefully and patients may have a negative ECG stress test. Thus, in a patient with exertional syncope, if the echocardiogram cannot convincingly show the origin of the coronary arteries, CT angiography of the coronary arteries should be performed. Patients have excellent outcomes after surgical repair, which can include unroofing the vessel from its intramural course.

Long QT Syndrome

Long QT syndrome (LQTS) is an inherited channelopathy affecting 1:2500 patients. Alterations in the potassium and sodium channels result in ventricular repolarization abnormalities and a predisposition toward the development of ventricular arrhythmias. The incidence of cases of SCD caused by LQTS in young athletes is estimated to be from 0.5% to 8%.[19–21] Diagnosing LQTS can be complex. In general, a QTc of more than 470 milliseconds in males and more than 480 milliseconds in females requires further investigation (**Fig. 4**).[22] Persons with LQTS may present with syncopal events during periods of stress, emotion, exercise, swimming, loud auditory stimuli, or relative bradycardia (ie, during sleep or rest), depending on the subtype of LQTS that the patient has.

There are several challenges with LQTS diagnosis, because one-third of the patients with LQTS may have normal QT interval at baseline and 10% to 15% of healthy individuals may have QTc greater than 440 milliseconds. In a study of pediatric ED patients with presyncope/syncope, one-third had QTc values of 440 milliseconds or greater. Of the patients who followed up with a pediatric cardiologist, no patient received a diagnosis of LQTS with normalization of QTc values.[23] Although isolated finding of borderline QT intervals on an ECG obtained after a syncopal episode must be interpreted with caution, it is prudent to refer these patients to a pediatric cardiologist for further evaluation. Treatment of this disorder includes avoidance of triggers, avoidance of QT-prolonging medications (visit http://www.qtdrug.org for comprehensive lists) β-blockers, and ICD placement.

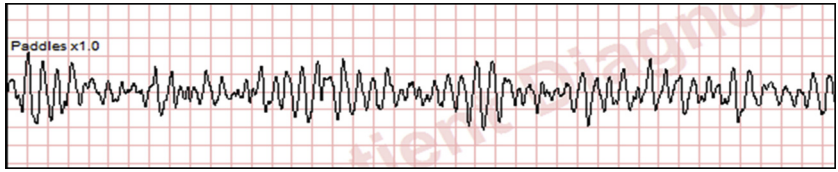

Fig. 3. Ventricular fibrillation in a young athlete with anomalous left coronary artery from the right sinus who collapsed on the field while playing.

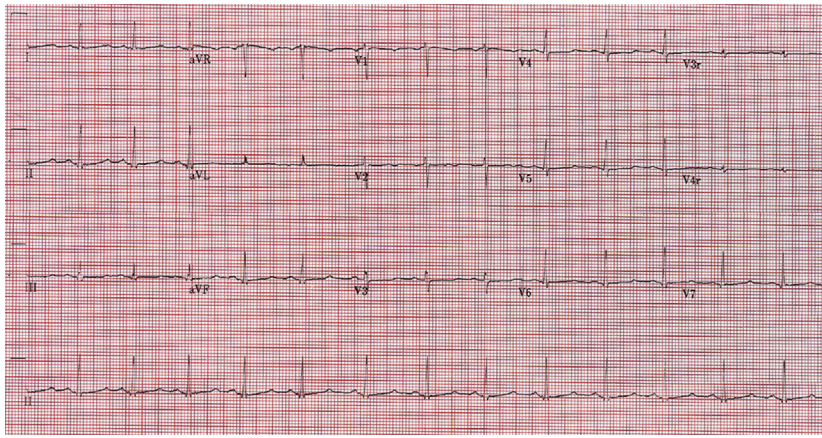

Fig. 4. ECG showing LQTS.

Brugada Syndrome

Manifested by right bundle branch block and ST elevation in V1 to V3 (**Fig. 5**), Brugada syndrome (BS) could be responsible for 4% of all SCD and up to 20% of SCD in structurally normal hearts. Arrhythmias, fast polymorphic ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF), can occur at any age. Patients can present with palpitations, dizziness, syncope, nocturnal agonal respiration, or aborted SCD. Arrhythmias occur at rest and when vagal tone is augmented such as nighttime during sleep. Eighty percent of patients with VT/VF have a history of syncope. Fever is another important trigger for arrhythmias in BS. Although fever itself can be associated with orthostatic hypotension and syncope, ECG should be carefully evaluated to rule out BS.[24] Patients with BS should be admitted for observation during febrile illness and should avoid triggers. Medications such as quinidine and ICD placement are the mainstays of therapy (see http://www.brugada.org for medications to avoid in patients with BS).

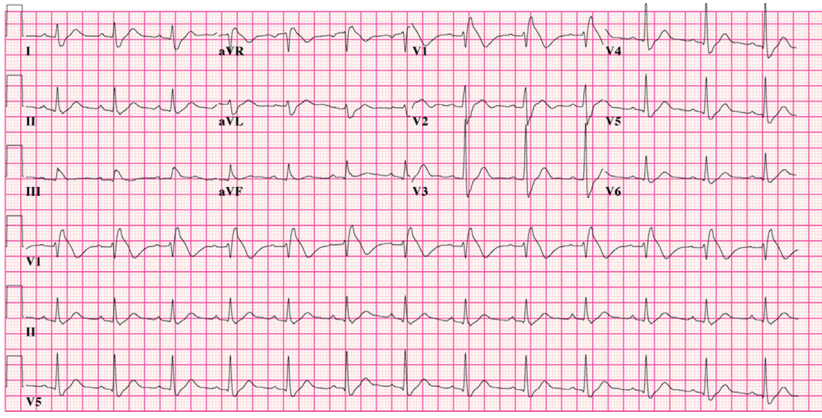

Fig. 5. ECG of Brugada syndrome: type 1, the most common, is characterized by >2 mm J point elevation followed by down-sloping ST segment and negative T waves in the right precordial leads. (*Courtesy of* Dr P.G. Postema, Amsterdam, Netherlands and ECGpedia.org.)

Catecholaminergic Polymorphic VT

Catecholaminergic polymorphic VT (CPVT) is another rare cause of sudden death among persons with structurally normal hearts, with an estimated prevalence of 1:10,000 persons.[25] It is an inherited disorder, with both autosomal-dominant and autosomal-recessive forms. Most events occur in the first and second decade of life. Patients present with syncope/SCD caused by bidirectional VT (**Fig. 6**) or polymorphic VT triggered by exercise or emotional stress. Baseline ECG is usually normal, and a stress test must be obtained. Treatment of this disorder includes β-blockers, trigger avoidance, verapamil, and ICD placement.

Arrhythmogenic Right Ventricular Dysplasia or Cardiomyopathy

Arrhythmogenic right ventricular dysplasia (ARVD) is an autosomal-dominant genetic cardiomyopathy affecting 1:2000 to 1:5000 people, which causes ventricular arrhythmias, resulting in syncope or sudden death.[26] Exercise is a common trigger, and the disease usually presents in the second to fifth decade of life. There is progressive replacement of right ventricular myocardium with fibrofatty tissue, which is diagnosed by MRI. The diagnosis of ARVD can be difficult, and clinical criteria should be used to aid in the diagnosis. Baseline ECG (**Fig. 7**) is abnormal in 90% of the patients. Competitive sports are contraindicated for these patients, and all symptomatic patients should receive an ICD.

Myocarditis

Myocarditis can also result in SCD secondary to fatal arrhythmias, which can occur in both the acute and healing phase of the illness.[27] Any patient presenting with syncope with recent history of febrile illness, rash, fatigue, and chest pain should be evaluated for myocarditis. Clinical examination may be normal, or patients may have a regurgitant murmur, pericardial rub, and muffled heart sounds on auscultation. ECG can show ventricular ectopy or nonspecific ST/T wave abnormalities. Cardiac enzyme levels may be increased, and echocardiogram may show decreased function, atrioventricular (AV) valve regurgitation, or pericardial effusion. Delayed gadolinium-

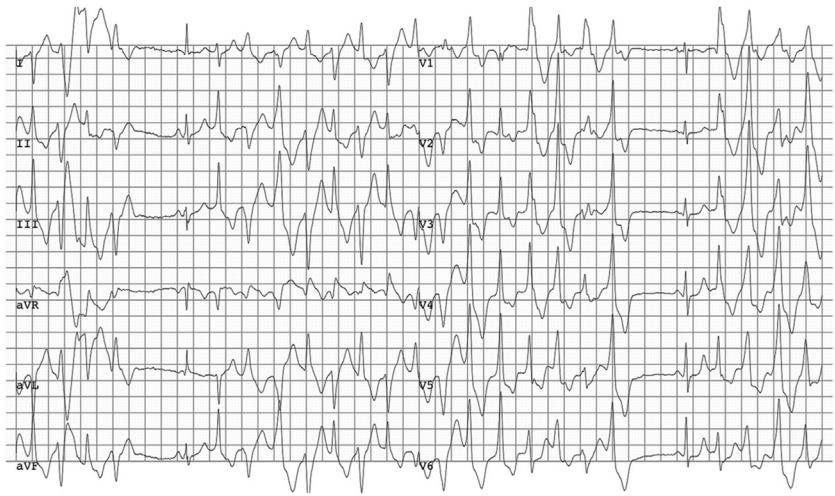

Fig. 6. ECG showing CPVT. (*Courtesy of* Dr van der Werf, Amsterdam, Netherlands and ECGpedia.org.)

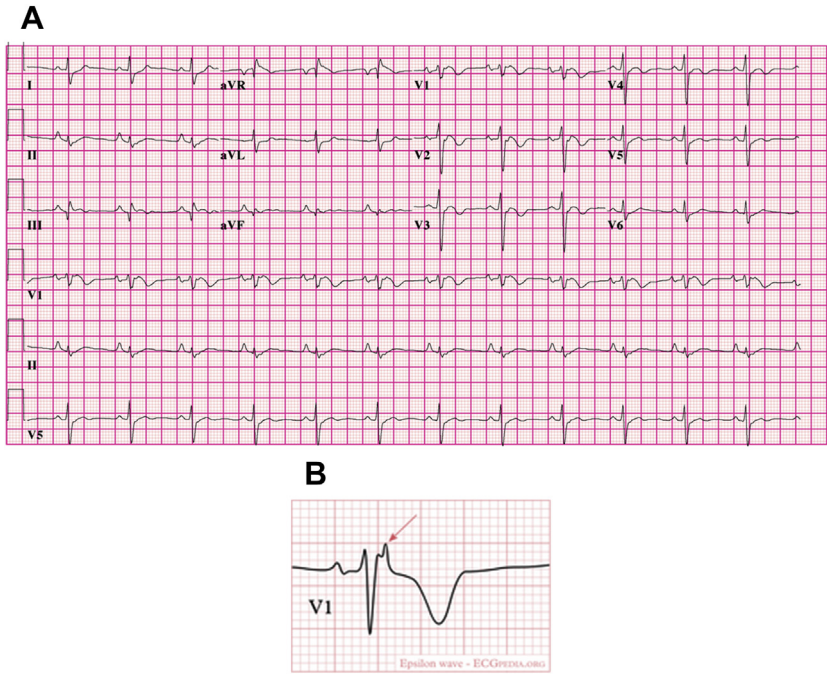

Fig. 7. (*A*) ARVD ECG: note the inverted T waves in the right precordial leads, late potentials (ε waves), widened QRS complex in right precordial leads and prolonged S wave upstroke in V1 >55 milliseconds (*B*) V1 shown with ε wave. (*Courtesy of* ECGpedia.org.)

enhanced cardiac MRI has high sensitivity and specificity in diagnosing this condition. Treatment is mostly supportive; however, a subset of patients develop dilated cardiomyopathy, which may require medical management or cardiac transplant. Patients should avoid all competitive sports for 6 months after the onset, and they should be evaluated for arrhythmias and residual cardiac dysfunction before resuming training and competition.

Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White syndrome (WPW) is a result of an accessory pathway with both antegrade and retrograde conduction properties (**Fig. 8**A). Prevalence of WPW is estimated to be 1 to 3/1000 individuals, with an incidence of SCD of 0.2 to 15 per 1000 patient years.[28] The mechanism of SCD is rapid antegrade conduction over the accessory pathway in the setting of atrial fibrillation, resulting in VF. Any patient presenting with symptoms of palpitations or syncope who has irregular wide complex rhythm should be assumed to have atrial fibrillation with WPW (see **Fig. 8**B). Catheter ablation is a safe and usually effective treatment option. All patients who present with WPW, even if asymptomatic, should be referred to a pediatric cardiologist for risk assessment and further management.

Postoperative Arrhythmias in the Setting of Repaired Congenital Heart Defects

A major success story of pediatric cardiology is that more patients with complex congenital heart defects (CHD) survive into adulthood. Arrhythmogenic substrate created by the defect itself or from the surgery predisposes these patients to cardiac

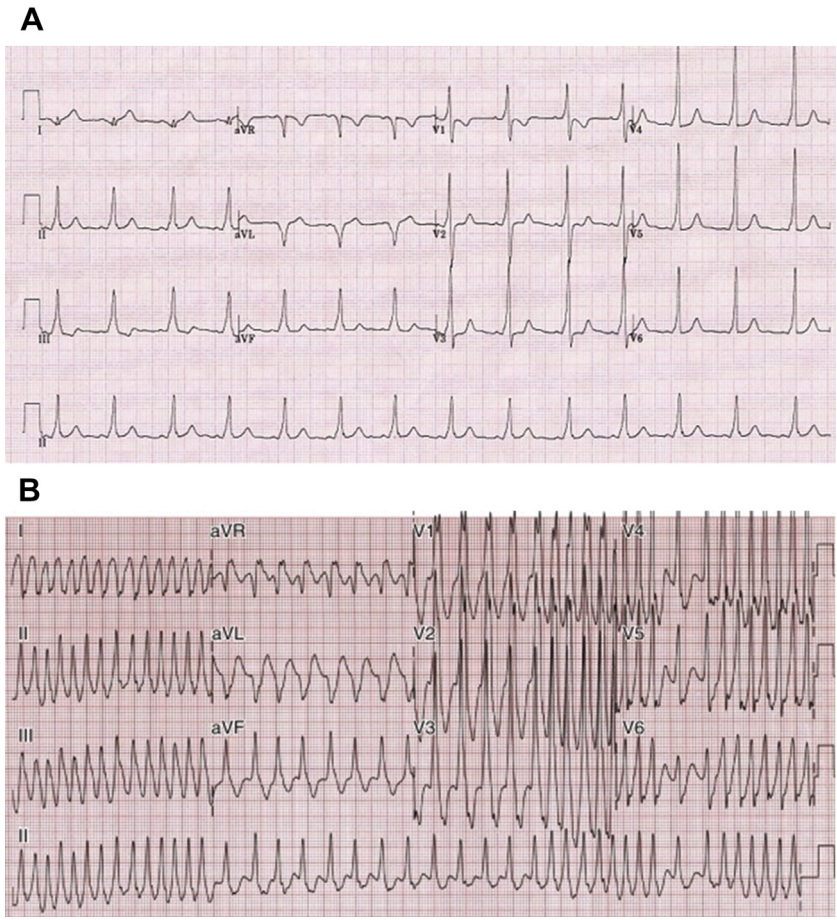

Fig. 8. (*A*) WPW ECG: note the pre-excitation or δ wave and short PR interval. (*B*) Pre-excited atrial fibrillation.

arrhythmias (**Fig. 9**). Patients with Senning/Mustard and Fontan procedures are likely to have atrial arrhythmias and sinus node dysfunction. Patients after tetralogy of Fallot repair are predisposed to both VT and atrial flutter. Heart block can occur after ventricular septal defect or AV canal repair. Any syncopal episode in a patient with previous cardiac history or surgery should be carefully evaluated for these arrhythmias, which can be hemodynamically compromising. Treatment of these dysrhythmias is complex and should be undertaken by a pediatric cardiologist.

Migraine

Migraines affect as much as 8.6% of the pediatric population.[29] Although commonly described as paroxysms of pain associated with nausea, vomiting, or abdominal pain and relieved by sleep, there are variants that can present with t-AMS; 3% of migraines are acute confusional migraines.[30] This diagnosis should be considered in patients with a family history of migraines, a personal history of migraines, or a concurrent headache. Episodes can last from a few minutes to hours. Treatments for this type

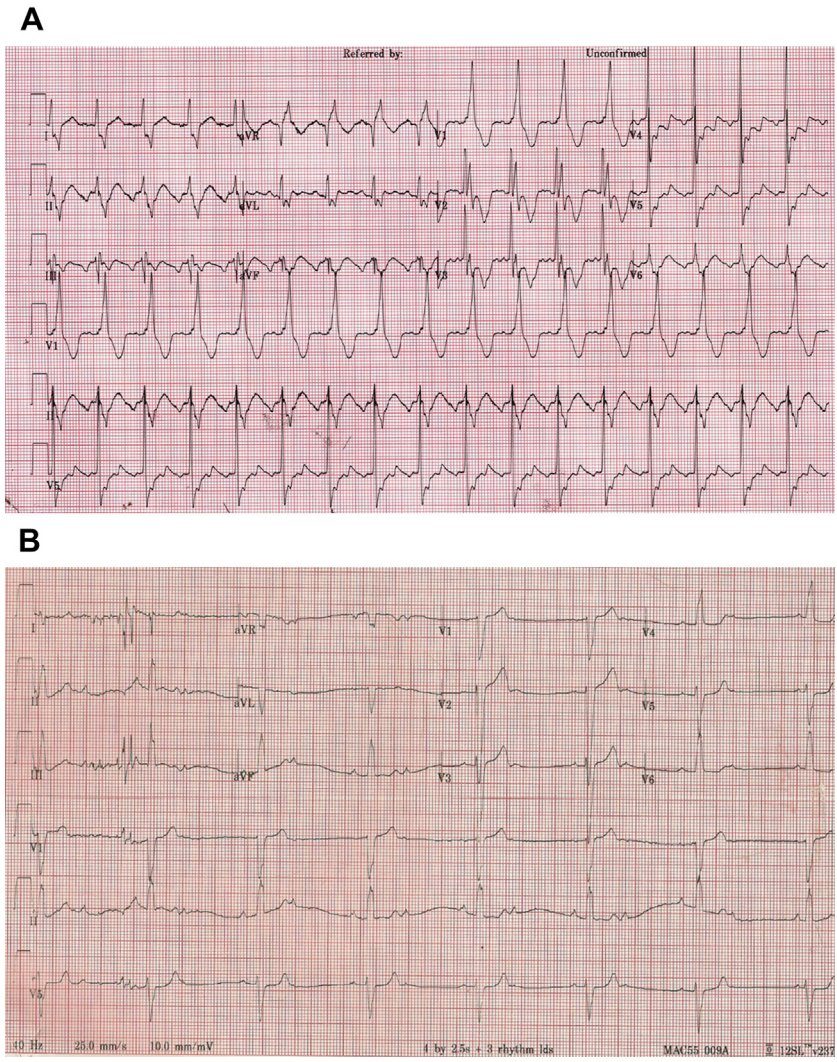

Fig. 9. (*A*) Atrial flutter in a 6-year-old patient after ventricular septal defect and interrupted aortic arch repair in infancy (*B*) Late complete heart block after AV canal repair in infancy.

of migraine are not well studied, given the rarity of the occurrence and because the diagnosis is made after return to baseline; however, 1 small study[31] implied that these episodes may be treatable with common migraine medications such as prochlorperazine.

Conversion

Conversion disorder and malingering are diagnoses of exclusion for patients who present with t-AMS. However, they are on the differential, especially in otherwise healthy adolescents, who present with recurrent syncopal episodes. The true incidences of

these causes are unknown; however, in studies of patients referred for further evaluation, between 10% and 20% were believed to have psychogenic causes of t-AMS.[32,33] Historical clues that can help with this diagnosis include occurrence during times of secondary gain and lack of self-injury. Although the role of head-up tilt table testing is controversial in the evaluation of reflex syncope, it can be useful in evaluating for conversion. In reflex syncope, whe n the patient is tilted upright, their BP should decrease and they should experience a syncopal event. Conversely, conversion can be diagnosed if the patient experiences a syncopal event when tilted, without a corresponding change in BP.[34]

CAUSES FOR P-AMS

Infants and Young Children

As noted in the introduction, p-AMS occurs when the brain has a structural issue, an inadequate supply of oxygen, an imbalance in key electrolytes, inflammation from metabolic or infectious causes, or problems with the way electricity is conducted through the tissue. Because of their higher surface area/volume ratio and increased metabolic rate in combination with small glycogen stores and inefficient gluconeogenesis, infants are at higher risk for AMS from inadequate perfusion and hypoglycemia. This situation is true even from mild insults such as gastroenteritis, feeding intolerance, fevers, and so forth. In addition, the risk of direct infection of the central nervous system (CNS) is higher because of an immature immune system. Metabolic abnormalities are usually diagnosed at this time of life as well. Thus, the incidence of AMS is higher in infants.

Sepsis

When any young infant presents to a physician with a deviation from their normal activity, infection is always a concern. Sepsis alone in a neonate can cause AMS for several reasons: poor cerebral perfusion from distributive shock; insufficient glucose delivery to the brain from hypermetabolic state in the setting of low reserves; metabolic derangements such as severe metabolic acidosis, respiratory acidosis, or hyponatremia; and direct infectious involvement of the brain. Fever is not always present, even in the setting of overwhelming infection.

Inborn errors of metabolism

Most children who are born in hospitals in the United States undergo extensive testing for inborn errors of metabolism (IEM). Thus, it is not often that a clinician comes into contact with a previously undiagnosed problem. However, there are situations in which a child may have a metabolic disorder that is unknown, especially in the first few days of life, and it is imperative that clinicians think of IEM in infants who present with p-AMS. IEMs that present with AMS, especially in the first few days of life, are the organic acidemias or urea cycle disorders. These disorders of normal protein catabolism lead to profound acidosis or a buildup of neurotoxic ammonia. These infants present in the first few days/weeks of life with lethargy and vomiting. Rapid realization of the presence of an IEM, and prompt treatment, leads to marked improvement in morbidity and mortality.[35] Before initiation of treatment, evaluation of these patients should include blood and urine for amino acid levels, a comprehensive metabolic panel, blood gas, and ammonia level. Rapid initiation of treatment is paramount for survival and for optimal neurologic outcome. This treatment includes shutting down the catabolic state regardless of blood sugar with the administration of glucose-containing intravenous (IV) fluids. If the ammonia level is increased, the patient requires emergent hemodialysis.

Nonaccidental trauma

In infants and young children, the possibility of nonaccidental trauma (NAT) should always be considered. The incidence of inflicted brain injury in children younger than 2 years is slightly higher and associated with a worse outcome than that of accidental brain injury.[36,37] This situation can be challenging for practitioners, because these children may have few signs of external trauma. There may be associated symptoms and signs, such as irritability, focal neurologic deficits, or a bulging fontanel; however, these findings do not need to be present for clinicians to consider intracranial injury.[36] It is always important to consider NAT in an infant who presents with p-AMS, regardless of signs of trauma. Although judicious use of CT is always recommended, the exception comes in the evaluation for NAT, for which it is the most rapidly available and sensitive examination for acute intracranial hemorrhage. After ensuring that there is no acute neurosurgical emergency, if there is a concern for trauma, these infants should be admitted for skeletal surveys, retinal examinations, and potentially an MRI to evaluate for more subtle or chronic injuries.

Intussusception

The classic presentation of intussusception is an infant with colicky abdominal pain and bloody stool. However, AMS and hypotonia are well-described presenting symptoms; in 1 study,[38] 19% of all patients with intussusception presented with lethargy or somnolence. Although intussusception can occur in older patients, AMS is a presenting symptom more commonly seen in the infant age group. One theory for this finding is endogenous opioid release causing AMS.[39] Infants with intussusception who present with AMS often have symptoms of gastrointestinal illness, such as vomiting, irritability, abdominal pain, melena, or palpable mass. In the evaluations of patients for intussusception, ultrasonography has proved to be a readily available, safe, and sensitive tool. If findings are positive, patients should receive a therapeutic air enema performed by a radiologist.[40]

Infections (shigellosis)

One of the known complications of shigellosis is seizure or encephalopathy not secondary to CNS infection or as a direct effect of the Shiga toxin. In 1 study of 71 pediatric patients with *Shigella* infections, 9% were unconscious and 5% had documented seizure. Children with AMS tended to have shorter durations of illness, higher fevers, more severe dehydration, and lower serum sodium levels.[41,42] Diagnosing *Shigella* involves isolation of the bacteria from the stool or blood. Although shigellosis is usually a mild, self-limited disease, presentation with AMS should be treated with antibiotics. Although resistance is increasing, first-line therapy includes trimethoprim-sulfamethoxazole or ampicillin.[43]

Encephalitis

Encephalitis means inflammation of the brain. Although encephalitis is often thought of as an infectious process, there are also parainfectious and inflammatory causes. Infectious causes cause direct pathogen-mediated cell death and mechanical injury, and both infectious and parainfectious causes can cause immune-mediated effects, including demyelination and neurotransmitter disturbances. Fever is not always present, even with a later confirmed infectious source.[44] Emergent lumbar puncture and initiation of broad-spectrum antibiotics and antivirals are indicated in encephalopathic patients in whom infection is a concern. When the meninges are involved, patients can have associated headache, photophobia, and stiff neck; however, when they are not inflamed, these helpful clues may be absent. Thus, encephalitis must always be considered as a cause of p-AMS. Acute demyelinating

encephalomyelitis is a well-described cause of noninfectious encephalitis. It is most commonly described after an antecedent infection, and it can present with or without fever. It is a diagnosis made by MRI after negative serologic evaluation.

Seizure

Seizures are common, with an annual incidence of 84 per 100,000 persons, half of whom go on to develop epilepsy.[45] Although epilepsy is a complex diagnosis, with many subtypes and presentations, the focus of this section is nonconvulsive status epilepticus (NCSE) and the postictal state. NCSE can be difficult to identify clinically. These patients can present with stable AMS and a waxing and waning mental status or be critically ill. In 1 pediatric retrospective study,[45] the incidence of NCSE in patients with AMS was 14%. Although NCSE is most common in patients with a known seizure disorder, it should be considered in all children with AMS without obvious traumatic, metabolic, structural, or infectious cause. Emergent bedside EEG is the diagnostic study of choice, and treatment should include antiepileptic drugs and potentially barbiturate anesthesia.[46] A prolonged postictal state is also a consideration in patients with p-AMS.[47] Prolonged postictal states can persist for days, especially in patients who have had multiple complex seizures, who have developmental delay or cortical abnormalities, and in those with underlying psychiatric diagnoses.[48]

Metabolic derangement (glucose, sodium)

Abnormal blood glucose levels, high or low, can cause AMS. In the case of hypoglycemia, there are 2 mechanisms for this process: autonomic dysfunction and neuroglycopenia. Although the most common cause of hypoglycemia in older children is a misadventure with insulin, in younger infants, increased metabolic rate and metabolic stresses such as infections or dehydration can lead to profound hypoglycemia. In hyperglycemic patients with diabetic ketoacidosis (DKA), AMS from cerebral edema is an ominous sign. It occurs in only 1% of episodes of DKA but it has a high mortality (20%–50%).[49] The mechanism of this AMS is believed to be secondary to a combination of multiple metabolic abnormalities, including dehydration and decreased cerebral perfusion caused by circulatory collapse; acidosis; hyperosmolality; and decreased glucose use by cerebral tissue.[50,51] Treatment of this disorder involves careful insulin administration and restoration of euvolemia.

Because brain volume is regulated by equal osmolality of intracellular and extracellular sodium, rapid changes in sodium, most commonly hyponatremia, can cause p-AMS. In children, the cause of hyponatremia can come from total fluid losses (gastroenteritis, postoperative), excessive sodium loss from the kidneys (mineralocorticoid deficiency, cerebral salt wasting), excessive water retention by the kidneys (SIADH [syndrome of inappropriate antidiuretic hormone secretion]), or conditions in which there is excessive free water (cirrhosis, nephritic syndrome, or heart failure).[52] Young children are at increased risk of hyponatremic encephalopathy secondary to a larger brain/intracranial volume ratio, with less room for swelling.[52] The correct historical clues, in the presence of p-AMS and marked hyponatremia, are diagnostic for this condition. Normalization of sodium levels is critical but must be performed carefully and slowly to avoid rapid osmotic shifts.

Intracranial tumor/mass

Space-occupying lesions of the brain, whether blood or a mass or a combination, cause depressed level of consciousness by the same mechanism. There can be mass effect, which directly increases intracranial pressure, obstruction of drainage of the cerebral spinal fluid, or acute herniation.[53] It is critical for physicians to consider stroke in children, in whom the incidence equals that of brain tumor (2/100,000).[54] Half

of strokes are hemorrhagic, and 50% of those present with AMS.[55] Imaging with CT is the first step in diagnostic testing and should be followed by emergent neurosurgical consultation.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES), formally hypertensive encephalopathy, is an increasingly recognized disease thanks to the ready availability of MRI studies. PRES occurs when acute hypertension exceeds the vasoconstrictive and regulatory processes in the brain, causing a vasogenic edema. Patients can present with headache, seizure, and AMS. In children, there is often an underlying cause; nephrotic syndrome, Henoch-Schönlein purpura, and therapies for malignancies are some of the many culprits.[56] The treatment of PRES includes cessation of offending agents and prompt management of BP.

APPROACH TO THE PATIENT WITH TRANSIENT AMS

Patient History

Accurate, detailed, and thorough history is the most important part of the evaluation of a patient presenting to the ED with t-AMS and should establish the diagnosis correctly. Every effort should be made to obtain a direct history from the eyewitnesses, asking questions pertaining to circumstances before the attack, about the actual episode and details of events after the episode. An age-based approach to patients with t-AMS is critical to avoid excessive workups and not miss any life-threatening causes. In neonates, one should consider sepsis and ask about sick contacts, group B β *Streptococcus* status of the mother, and temperature instability. A broad family history is important (**Box 3**C). Indicators of seizure include abnormal movements, eye rolling, and a postictal period. As the patient enters toddlerhood, BHSs enter into the differential. The clinician needs to ask about temporal proximity to an emotionally stressful event or minor trauma. A patient or family history of migraines can point a clinician toward an atypical or acute confusional migraine.

An important distinction to make for the diagnostic workup is whether this event was true syncope and if so, was it a common, benign reflex syncope episode or a more ominous cause. Many of the children with cardiovascular disorder who go on to experience SCA have syncope or presyncope as a warning symptom. Identifying this small subset amongst all patients who present with syncope is difficult. See **Box 3** for historical features that can help differentiate benign neurally mediated syncope from cardiac syncope. In contrast to reflex syncope, which is often triggered by specific events and has premonitory symptoms, individuals with syncope from a cardiac disorder at risk for SCA usually have an abrupt collapse without warning, because of the onset of a potentially lethal ventricular arrhythmia. Syncope occurring during exercise is an ominous sign and warrants a high index of suspicion for underlying cardiac disease. Distinguishing between neurocardiogenic syncope and seizures is a common clinical dilemma faced by care providers. **Table 2** provides diagnostic clues differentiating syncope from seizure. A careful history of the event and details of the past medical and family history should eliminate most of the causes of cardiac syncope.

Physical Examination

After an episode of t-AMS, the patient likely has a normal physical examination. As with all physical examinations, careful attention must be paid to the vital signs. Hypothermia as well as hyperthermia can be indications of sepsis in neonates. Heart rate and BP should be compared with age-appropriate norms. Neurologic examination

Box 3
Historical features that may help differentiate reflex syncope versus cardiac syncope. (*A*) Clinical feature of neurally mediated syncope; (*B*) clinical features of cardiac syncope; and (*C*) family history features concerning for cardiac syncope

A. Reflex syncope
   1. Long history of recurrent syncope
   2. Absence of heart disease
   3. Typical triggers (**Table 2**) such as prolonged standing in hot, crowded places
   4. After exertion
   5. With head rotation or pressure on carotid sinus (tight collars, shaving, backing up a car)
   6. Associated with nausea or vomiting
   7. Prodrome of lightheadedness, dizziness, diaphoresis, nausea, and tunnel vision

B. Cardiac syncope: red flags
   1. Presence of heart disease or previous cardiac surgery
   2. Family history of hereditary cardiomyopathy or channelopathy (**Box 2**)
   3. Sudden onset of palpitation, shortness of breath, or chest pain followed by syncope
   4. Episodes during exertion, swimming, or supine
   5. ECG abnormality
   6. Episodes brought on by sudden startle or loud noise such as alarm clock (LQTS)
   7. Acute or subacute history of febrile illness, exercise intolerance, or fatigue (cardiomyopathy, myocarditis)
   8. Abrupt syncope with no premonitory symptoms
   9. Injury with syncope
   10. Event triggers: extreme emotional stress (LQTS)
   11. Young age at presentation (<10 years of age, especially <6 years of age)
   12. Unexplained seizure in the past

C. Cardiac syncope: red flags in the family history
   1. Sudden unexpected unexplained death at a young age (<30 years)
   2. Unexplained fainting spells or seizures
   3. Unexplained driving or drowning accidents
   4. Sudden infant death syndrome
   5. Congenital deafness
   6. Hereditary cardiomyopathies (HCM, dilated cardiomyopathy, ARVD)
   7. Hereditary channelopathies (LQTS, Brugada, CPVT, short QTS)
   8. Pacemaker or defibrillator implants at a young age
   9. Marfan syndrome

can be difficult in young infants; careful attention to development, tone, and pupil examination is a must. Cardiovascular examination should focus on evaluation for dysrhythmia and murmurs. Because infants with ALTEs have a higher frequency of NAT, these patients should be examined from head to toe to evaluate for other signs

Table 2
Clinical clues helpful in differentiating syncope from seizures

	Syncope	Seizure
Triggers	Typical	Rarely (flashing lights)
Prodrome/aura	1. Sweating and pallor 2. Nausea, vomiting, and abdominal discomfort 3. Lightheadedness, blurring	1. Rising sensation in abdomen 2. Smell
Movements	1. Last few seconds, <15 s 2. Asynchronous 3. Nonrhythmical 4. After fall and unconsciousness	1. Last ~1 min 2. Synchronous 3. Rhythmical 4. Before fall
Flaccidity	Often complete	Unlikely
Tongue bite	1. Rare 2. Middle	1. Common 2. On the side
Recovery	1. Immediate clear headedness 2. Nausea, vomiting and pallor	1. Prolonged confusion 2. Muscle aches and headaches

Adapted from Moya A, Sutton R, Ammirati F, et al, The Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC). Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30(21):2655; with permission.

of trauma. Physical examination is unremarkable in all cases of reflex syncope and most cases of cardiac syncope. However, clinical features (detailed in **Box 4**) can impart important diagnostic clues to a potentially serious cause of syncope.

Imaging and Additional Testing

In neonates, a full septic evaluation should be considered if there are any changes from normal behavior. If there is concern for NAT, if there are any neurologic abnormalities on examination, or if the patient has any complaint of headache, a CT scan of the head should be performed. A finger-stick glucose measurement is obtained for many patients who present after an episode of t-AMS; however, this is unlikely to be helpful, because a patient who has returned to baseline is unlikely to be persistently hypoglycemic. Hemoglobin should be measured to diagnose anemia, and a urine pregnancy test in the adolescent female is mandatory. Although the workup for an ALTE is controversial, and beyond the scope of this article, an ECG should be obtained to evaluate for dysrhythmia potential.

Box 4
Physical examination findings that indicate cardiovascular cause of syncope

Key points to assess and to look for in physical examination

1. Heart rate and orthostatic BP
2. Sternotomy scar points toward past cardiac surgery, device pocket
3. Right ventricular heave with loud second heart sound suggest pulmonary hypertension
4. Gallop heard in dilated cardiomyopathy and congestive heart failure
5. Midsystolic murmur that increases in intensity with standing suggestive of HCM
6. Systolic murmur of aortic stenosis
7. Tumor plop of left atrial myxoma

Careful clinician judgment has to be used when considering imaging, because all modalities carry some inherent risks. CT exposes children to radiation and should be reserved for concerns of trauma or intracranial bleeding. For other possible intracranial causes of t-AMS, MRI might be a better option, because of its increased sensitivity for small and posterior lesions, keeping in mind that in young children, this test requires sedation and cannot be performed quickly.

The single most clinically useful and cost-effective test to evaluate syncope is the 12-lead ECG (**Box 5**). All patients presenting to the ED with syncope should receive ECG with a rhythm strip. In 1 review of 480 pediatric patients who presented with syncope,[57] a cardiac cause for syncope was identified in 22 patients (5%), 21 of whom were identified by an abnormal history (exercise-induced syncope or family history of sudden death), physical examination, or ECG. If the history and physical examination are typical for neurocardiogenic syncope and the ECG is normal, further testing generally is not needed.

Referral to a pediatric cardiologist should be for atypical history, red flags, abnormal ECG, and abnormal murmurs, as detailed in **Boxes 3–5**. Additional testing may include continuous in-hospital ECG monitoring when the patient is at high risk for a life-threatening arrhythmia, Holter monitoring, loop recorders, and echocardiography to assess for cardiac function and structural abnormalities. The role of tilt table testing is debatable, because of issues of low reproducibility and a high false-negative rate. Exercise stress testing is important in evaluating exertional syncope. An electrophysiology study may sometimes be indicated in patients with structural heart disease.

APPROACH TO THE PATIENT WITH P-AMS

Patient History

As with any initial presentation, physicians must assess the patient for respiratory and cardiovascular stability and they must establish a Glasgow Coma Score if trauma is considered. Once the patient has been stabilized, the provider can move on to a more detailed history and physical examination. In infants, key questions focus on signs or symptoms of infection (fever, sick contacts, cough, coryza, vomiting, diarrhea, and rashes), a family history, and a birth history to evaluate for the potential of

Box 5
ECG abnormalities to look for in a patient presenting with syncope

1. LVH, ST/T wave abnormality
2. Nonsustained VT
3. Wide QRS (left bundle branch block, right bundle branch block, bifascicular block, intraventricular conduction delay)
4. Bradycardia, AV block, or prolonged pauses
5. Corrected QT interval to assess for LQTS, short QT syndrome
6. δ wave suggestive of WPW
7. Right bundle branch block + ST elevation in V1 to V3 (Brugada)
8. Negative T waves in right precordial leads and ε waves suggestive of arrhythmogenic right ventricular cardiomyopathy
9. Q waves suggesting myocardial infarction, HCM

undiagnosed IEM, and a delicate scrutiny for NAT. Questions regarding abdominal pain, vomiting, and character of stool are also important when evaluating an older infant for intussusception.

As the patient gets older, encephalitides becomes a more common possibility. Again, toxicologic causes of AMS are beyond the scope of this article but should be considered. Infectious symptoms should be elicited, as previously described in infants, and special care should be taken to elicit clues that suggest a diagnosis of PRES, nonclinical status epilepticus, DKA, or hypoglycemia. Recent history of head trauma or headaches should alert the clinician that a space-occupying lesion may be present in the brain, whether blood, mass, or excessive CSF.

Physical Examination

The most critical portion of the physical examination in a patient with AMS is careful evaluation of the vital signs. Primarily, the clinician needs to focus on adequate respirations (with normal respiratory rate and oxygen saturations) and perfusion (evaluation of pulses, heart rate, and BP). Fever can be a marker of both infectious cause as well as intracranial disease. Hypertension is concerning for PRES or increased intracranial pressure and tachypnea can indicate profound hyperglycemia. Once the patient has been stabilized, a careful neurologic, cardiovascular, and respiratory examination should be performed. The neurologic examination may be limited with an uncooperative, altered or comatose patient, and small focal neurologic deficits can be missed. Once airway, breathing, and circulation are established to be stable, the physician should consider the diagnostic workup while examining the patient. A change in mental status requires prompt and efficient assessment and evaluation, rather than a standard linear approach to history taking and physical examination, with subsequent testing.

Imaging and Additional Testing

Although the clinician obtains many clues in the history and physical examination, these patients usually require extensive diagnostic testing as well as admission to the hospital. Blood glucose must be measured. All abnormalities should be addressed before moving on to the next stage of the evaluation. If an infectious cause is on the differential, especially in a young infant, cultures should be obtained quickly, such that IV antibiotics can be administered as quickly as possible. Thus, blood counts, blood cultures, urinalysis, urine cultures, and CSF for cell count, Gram stain, protein, glucose, and culture should all be obtained. Timely administration of antibiotics should not await successful lumbar puncture.

Unlike patients with t-AMS, all patients who present with p-AMS should have emergent imaging of the head. Unless the AMS clears with the administration of glucose, even a hypoglycemic patient should receive imaging because one never knows if the patient sustained an injury while altered. Whether the lumbar puncture should await normal head CT is controversial and outside the scope of this article.

If there is concern for an inborn error of metabolism, blood for a serum ammonia, amino acid levels as well as urine for organic acids need to be obtained before the administration of dextrose, because this may alter the results. If intussusception is on the differential, the evaluation can include a plain film radiograph series, ultrasonography of the abdomen, or in cases of high pretest probability, a prompt enema by a radiologist that is both diagnostic and therapeutic. To evaluate for nonclinical status epilepticus, an EEG is required.

SUMMARY

Although AMS, transient or persistent, can cause a great deal of anxiety for patients and providers, a rational approach to these patients is essential to avoid underuse or excessive use of testing. An age-based approach is important, because the various diseases are common in different age groups. In patients with t-AMS, differentiating true syncope from other causes is the first step; a stepwise approach, guided by the history and physical examination can then proceed. p-AMS, on the other hand, is a life-threatening presentation, and time is of the essence. The differential diagnosis is broad and, rather than trying to recall long lists of highly specific causes, it is more helpful to consider broad categories of disease: structural lesions, insufficient delivery of appropriate substrate to the brain, metabolic imbalance, inflammation, infection, and abnormal electrical activity. Maintaining a broad differential and evaluating for multiple diseases simultaneously is critical in the care of these patients.

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