ILLUSTRATIVE CASE

Atypical Altered Mental Status in a Toddler

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CASE

A 2-year-old girl presented with 2 days of altered mental status (AMS). Symptoms included increased sleepiness, irritability, aggression, decreased oral intake and urine output, as well as weakness and refusal to walk. Her history was negative for fever, cough, rhinorrhea, vomiting, diarrhea, rashes, seizurelike activity, recent head trauma, or other injuries. There were no known sick contacts or recent travels. She did attend day care. The family reported no medications in the home.

In triage, she was afebrile with a pulse of 125 beats per minute, respiratory rate of 21 breaths per minute, blood pressure of 103/79, and oxygen saturation of 100% on room air. On examination, the child was sleepy and difficult to arouse. Her neurologic examination was notable for irritability, delayed response to stimuli, ataxia, and a Glasgow Coma Scale of 14. There were no focal neurologic defects appreciated.

Question: What are the current recommendations for the evaluation of a child with AMS?

Discussion

AMS is defined as a change in a patient's awareness of self or how a patient interacts with their environment.[1,2] AMS is a complex presenting symptom with a wide range of severity and broad differential that varies by a patient's age (Table 1).

The basics of emergency management (including airway, breathing, and circulation) should guide any initial evaluation. A clinician must then attempt to distinguish between causes for AMS by using a systematic approach for evaluation and diagnostic testing. The mnemonic VITAMIN C (vascular, infectious, trauma, autoimmune/allergy, metabolic/mass lesion, idiopathic/iatrogenic, neoplasm, and congenital) can be used as a quick reminder of the potential causes of AMS.

A thorough history from family members and other sources including neighbors, prehospital personnel, or law enforcement is imperative.[3,4] A complete review of systems, as well as the patient's past medical history (including previous ingestions, recent medication changes, or propensity for infection or metabolic derangements), are also important in guiding management. Vital signs, particularly fever, can help point to an infectious cause; however, ingestions can also lead to significant vital sign abnormalities. Alterations in respiratory patterns may suggest toxic or metabolic derangements, whereas bradycardia and hypertension may point to increased intracranial pressure. The physical examination must include a complete neurologic examination focusing on

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TABLE 1 Breakdown of Common Causes of Both Transient and Permanent AMS by Age

Infants or Toddlers	School-Age Children	Adolescents
	Transient AMS	
Seizure	Seizure	Seizure
Trauma	Trauma	Trauma
Sepsis	Migraine	Psychiatric causes
BRUE	Syncope	Syncope
Breath-holding spells	—	—
	Persistent AMS	
Seizure	Seizure	Seizure
Trauma	Trauma	Trauma
Shock	Shock	Shock
Toxicologic	Toxicologic	Toxicologic
Electrolyte abnormality	Electrolyte abnormality	Electrolyte abnormality
Sepsis or encephalitis	Encephalitis	Encephalitis
Inborn errors of metabolism	Hyperglycemia or hypoglycemia	Hyperglycemia or hypoglycemia
Hypoglycemia	Brain mass	Brain mass
Breath-holding spells	Postictal state	Postictal state
Intussusception	Shigellosis	Posterior reversible encephalopathy syndrome

BRUE, brief resolved unexplained event; —, not applicable. (Reprinted with permission from MacNeill EC, Vashist S. Approach to syncope and altered mental status. *Pediatr Clin North Am.* 2013;60(5):1084)

Glasgow Coma Scale, tone, pupillary reflex, and extraocular movements, which can help identify possible intracranial lesions requiring immediate imaging.[2,5] Other important physical examination findings include meningismus, which should raise concern for meningitis and prompt discussion of a lumbar puncture (LP). Skin findings such as bruising should prompt further evaluation for intentional trauma.

Initial laboratory data should include a point-of-care glucose, electrolytes, complete blood cell count, blood gas, and urinalysis with urine toxicology screen. Cultures should be considered if there is concern for an infectious process. An electrocardiogram may be helpful to rule out ingestion of any cardiotoxic medications.[2] When there is concern for acute ischemia, hemorrhage, hydrocephalus, or a mass lesion, a head computed tomography scan is a useful first-line imaging modality to rapidly rule out potentially life-threatening causes of AMS.

CASE CONTINUATION

The patient's laboratory results were normal, including complete blood cell count with differential, electrolytes including serum glucose, and a negative standard urine toxicology screen. A computed tomography scan of the head was unremarkable. The patient was admitted for monitoring of her AMS. The morning after admission, the child continued to be difficult to arouse with persistent ataxia. She was also noted to have lower extremity hypertonia and mild nuchal rigidity. Because of her abnormal neurologic examination, nuchal rigidity, and persistent AMS, the decision was made to perform a diagnostic LP to assess for possible infectious causes.

Question: In which patients with AMS should an LP be performed?

Discussion

Although diagnostic tests such as head imaging are common practice in the evaluation of unexplained AMS, an LP to assess cerebrospinal fluid (CSF) is not standard practice. The primary indication for an emergent LP in a patient presenting with AMS is concern for a central nervous system infection.[6] Children with meningitis may present with variable signs and symptoms depending on age or developmental status. For example, infants can demonstrate restlessness and irritability, whereas lethargy or stupor is more likely in children and adolescents. AMS itself has been found to have low predictive value for meningitis.[7] Symptoms more predictive of meningitis, such as bulging fontanelle in infants, or neck stiffness, seizures, and high fever, would direct the clinician toward consideration of an LP. The CSF studies should include bacterial cultures as well as viral studies such as enterovirus polymerase chain reaction. Lyme serologies may also be considered, depending on the geographic region and season.[8] Additionally, an LP is indicated to help assess other causes of AMS including inflammatory diseases (ie, Guillain-Barre or multiple sclerosis) or idiopathic intracranial hypertension. Seizures are an important cause of AMS in children and many clinical practice guidelines have been developed to direct clinicians on the proper workup for first time seizures, including simple and complex febrile seizures.[9] Some patients with complex febrile seizures, such as those patients in status epilepticus or with a prolonged postictal course, may benefit from this procedure.[10]

CASE CONTINUATION

The patient's CSF counts were appropriate for age, her CSF culture had no growth, and the results of an enterovirus polymerase chain reaction were negative. Without a clear infectious cause for her symptoms, the team contacted the local Poison Control with concern for possible ingestion. Although all atypical agents may cause sedation and vital sign abnormalities, aripiprazole was suggested as the possible ingested medication given her normal vitals, increased tone, and lethargy. Other potential side effects of atypical antipsychotics include electrocardiogram changes, specifically QRS widening and QTc prolongation, seen in quetiapine and ziprasidone, respectively.[11] After multiple conversations with the patient's family by numerous members of the team, it was discovered that several medications

previously not reported were present in the home, including aripiprazole, ziprasidone, and escitalopram. These medications were prescribed to the patient's older sister and often left out on the kitchen counter. The family had not initially reported these medications because they felt they were always kept out of her reach.

Drug levels were sent for the medications listed, and the patient was found to have an aripiprazole level of 609 ng/mL (therapeutic levels in adults have been reported as 150–210 ng/mL) at more than 48 hours after the approximate time of ingestion.[12] Although these drug levels are often a send-out laboratory test, they were easily obtained in a community-hospital setting. Over her 4 day hospital course, the child was provided supportive care and monitored with serial examinations. Child Protective Services was contacted regarding the unintentional ingestion and met with the family for home safety planning, which included a medication lockbox. At the time of discharge, the child was at her neurologic baseline and walked out of the pediatrics unit without difficulty.

Question: What is known about aripiprazole ingestions in the pediatric population?

Discussion

Aripiprazole is a second-generation antipsychotic medication first approved for use by the US Food and Drug Administration in 2002 for the treatment of schizophrenia, bipolar mania, major depressive disorder, and Tourette's syndrome.[13] In 2009, the Food and Drug Administration expanded the approved use to include treatment of children and adolescents aged 6 to 17 years of age with autism spectrum disorders, specifically for the management of symptoms of irritability and aggression.[14] A recent review also found that aripiprazole is commonly prescribed in off-label use for pediatric patients with attention deficit disorder, depression, and pervasive developmental disorders.[15]

Children with aripiprazole ingestions may present with tachycardia and hypotension, but often present with age-appropriate vitals. Common presenting features include vomiting, lethargy, and somnolence, although ataxia, tremors, encephalopathy, seizures, and dystonic reactions have also been reported.[16] Suicidal ideation may be the initial presenting symptom for adolescents who have supratherapeutic aripiprazole levels, as opposed to the dystonia and somnolence seen in children, highlighting the variable presentations by age.[17] Symptoms can be prolonged by a long half-life or wax and wane, possibly because of higher bioavailability in children.[18]

Multiple case reports and case series have been published regarding aripiprazole ingestions in the pediatric population; however, the full extent of these ingestions may not be known given the often varied and nonspecific symptoms at presentation.[15,19–23] Recently, Young et al[16] reported 157 confirmed ingestions of aripiprazole in children <18 years old through the California Poison Control database from 2002 to 2006. Data obtained from the Maryland Poison Control indicate that from 2011 to 2016, there were 114 reported cases of unintentional ingestions of aripiprazole in children aged 0 to 19 years in the state, with ∼61% in children 5 years old and younger. Of the reported cases, 63% were due to an ingestion of a family member's medication (K.M.D., personal communication, 2016).

Question: When suspecting accidental ingestion, what are some ways to gather the necessary information to make a diagnosis and begin appropriate management?

Discussion

Accidental ingestions remain a significant cause of preventable harm, and at a national level there is a push to limit unintentional medication overdoses among children as part of the Healthy People 2020 initiative.[24] Both clinicians and parents should have a low threshold for contacting their local Poison Control because they can often provide timely and potentially life-saving recommendations for evaluation and management of ingestions, including suggestions for laboratories, diagnostic tests, imaging, and time frames for follow-up. Clinicians should first attempt to elicit the exact name of the suspected substance, active ingredients (most easily found if the original container can be evaluated), and concentration. The suspected amount consumed is also important because there is often a direct relationship with the volume consumed and the likelihood of an adverse clinical manifestation.[3] The 23 products or pharmaceuticals capable of killing young patients with even a small ingestion (1–2 teaspoons or 1–2 tablets) are listed in Table 2.[25] Other important pieces of information include time since ingestion, route of ingestion, expiration date, and any therapeutic interventions attempted.[3]

With any unwitnessed ingestion it is important to obtain information directly from caregivers regarding medications in the home, recent visitors, and any place the child may have visited in the last 24 hours.[26] This includes child care and relatives' homes, particularly grandparents or older relatives, who are more likely to have easily accessible prescription medications.[3] Eliciting this information from parents can be difficult because of fear of legal repercussions or concern about disclosure of personal medication use, including methadone or psychiatric medications[27]

TABLE 2 Pharmaceutical and Household Products Highly Toxic to Toddlers

Pharmaceutical and Household Products Highly Toxic to Toddlers			
Acetonitrile	Chloroquine	Hyoscyamine sulfate	Pennyroyal oil
Ammonium fluoride	Chlorpromazine	Imidazoline products	Quinine
Benzocaine	Clozapine	Lindane	Salt
Brodifacoum	Desipramine	Methadone	Selenious acid
Butyrolactone	Diphenoxylate	Methanol	Theophylline
Camphor	Hydrocarbons	Methyl salicylate	

(Reprinted with permission from Emery D, Singer J. Highly toxic ingestions for toddlers: when a pill can kill. *Pediatr Emerg Med Rep.* 1998;3.)

(Maryland Poison Control Center, personal communication, 2015). Clinicians should ask supportive, open-ended questions while stressing the importance of the information to properly care for their sick child. If concern persists for an ingestion without an etiology, multiple team members may need to ask family members at multiple time points. It can also be helpful to list all people in the home and ask about their individual medical problems to produce a list of possible medications or drug classes, as was done in this case. Approximately 500 000 calls are made to Poison Control each year after accidental ingestions by children who are undersupervised.[4,28] This emphasizes the importance of reproducing an accurate list of all medications prescribed to all people residing in the home to help quickly identify possible exposures.

CONCLUSIONS

Unlike other medications that have well-described presentations when taken in excess, the ingestion of aripiprazole has nonspecific symptoms and is not included as part of a standard urine toxicology screen. As was seen in this case, the "classic triad" leading to toxic ingestions includes improper storage of substances in the home, increasing childhood mobility, and transient distraction of caregivers.[3] To address this triad, families must be counseled on safe practices around the house, including appropriate storage of all medications out of reach, ideally in a safe, locked place. In addition, families should avoid any reference to medications as candy, as well as discussing the risks associated with the developmental milestones of walking and independent exploration.

Clinicians must have a high suspicion for an ingestion of an atypical antipsychotic medication in patients who present with persistent AMS when no other identifiable cause can be found. In all states, Poison Control is available by phone 24 hours a day, 7 days a week at 1 (800) 222-1222 to aid clinicians in diagnosis and management options, if there is direct concern for an ingestion, or unexplained presentations, including AMS.

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